In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 18-944V
Filed: February 21, 2023
PUBLISHED

CAMERON HARRIS, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	Special Master Horner Tetanus-diphtheria-acellular pertussis ("Tdap") vaccine; Meningococcal vaccine; Guillain-Barre Syndrome ("GBS"); Ruling on the record

Ronald Craig Homer, Conway, Homer, P.C., Boston, MA, for petitioner.
Christine M. Becer, U.S. Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

On June 29, 2018, petitioner, Cameron Harris,[2] filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2012),[3] alleging that his receipt of tetanus-diphtheria-acellular pertussis ("Tdap") and meningococcal vaccinations on July 8, 2015, caused-in-fact his Guillain-Barre Syndrome ("GBS"). (ECF No. 1.) For the reasons set forth below, I conclude that petitioner is entitled to compensation.

[1] Because this ruling contains a reasoned explanation for the special master's action in this case, it will be posted on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. *See* 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the ruling will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), petitioner has 14 days to identify and move to redact medical or other information the disclosure of which would constitute an unwarranted invasion of privacy. If the special master, upon review, agrees that the identified material fits within this definition, it will be redacted from public access.

[2] Petitioner was a minor when the petition was filed, so his mother filed the petition as his legal representative. Cameron reached the age of majority during the pendency of this claim and was substituted as petitioner on January 23, 2023. (ECF Nos. 78, 79.)

[3] Within this ruling, all citations to § 300aa will be the relevant sections of the Vaccine Act at 42 U.S.C. § 300aa-10-34.

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make several factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Finally – and the key question in most cases under the Program – the petitioner must also establish a *causal link* between the vaccination and the injury. In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable timeframe following the vaccination also specified in the Table. If so, the Table Injury is presumed to have been caused by the vaccination, and the petitioner is automatically entitled to compensation, unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1)(A); § 300 aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B).

In many cases, however, the vaccine recipient may have suffered an injury *not* of the type covered in the Vaccine Injury Table. In such instances, an alternative means exists to demonstrate entitlement to a Program award. That is, the petitioner may gain an award by showing that the recipient's injury was "caused-in-fact" by the vaccination in question. § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii). In such a situation, of course, the presumptions available under the Vaccine Injury Table are inoperative. The burden is on the petitioner to introduce evidence demonstrating that the vaccination actually caused the injury in question. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991).

The showing of "causation-in-fact" must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination was the cause of the injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause of the injury or condition, but must demonstrate that the vaccination was at least a "substantial factor" in causing the condition, and was a "but for" cause. *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). Thus, the petitioner must supply "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury;" the logical sequence must be supported by "reputable medical or scientific explanation, *i.e.*, evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). Petitioner may not receive a Vaccine Program award based solely on her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1).

In what has become the predominant framing of this burden of proof, the *Althen* court described the "causation-in-fact" standard, as follows:

> Concisely stated, [petitioner's] burden is to show by preponderant evidence that the vaccination brought about her injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury. If [petitioner] satisfies this burden, she is entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine.

Althen, 418 F.3d at 1278 (citations omitted). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting her causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. That expert's opinion must be "sound and reliable." *Boatmon v. Sec'y of Health & Human Servs*., 941 F.3d 1351, 1359-60 (Fed. Cir. 2019) (citing *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994)). The *Althen* court also indicated, however, that a Program factfinder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." 418 F.3d at 1280.

Generally, respondent bears the burden of demonstrating the presence of any alternative cause by preponderant evidence only if petitioner satisfies his *prima facie* burden. § 300aa-13(a)(1)(B); *Walther v. Sec'y of Health & Human Servs*., 485 F.3d 1146, 1150 (Fed. Cir. 2007). However, respondent may also present evidence relating to an alternative cause to demonstrate the inadequacy of petitioner's evidence supporting his case in chief. Nonetheless, petitioner does not bear the burden of eliminating alternative causes where the other evidence on causation is sufficient to establish a *prima facie* case under *Althen*. *de Bazan v. Sec'y of Health & Human Servs*., 539 F.3d 1347, 1352-53 (Fed. Cir. 2008); *Walther*, 485 F.3d at 1150.

II. Background Information Regarding GBS Cases in the Vaccine Program

GBS is an acute-onset, monophasic, polyneuropathy. (A.K. Meena et al., *Treatment Guidelines of Guillain-Barre Syndrome*, 14 ANN. INDIAN ACAD. NEUROL. 1 (2011) (Ex. 20); Roger Baxter et al., *Lack of Association of Guillain-Barre Syndrome with Vaccinations*, 57 CID 1 (2013) (Ex. II).) GBS is generally considered an autoimmune condition and is associated with several triggers, including infections and vaccination. (Baxter et al., *supra*, at Ex. II, p. 1.) Among published case series, approximately two-thirds of all cases are preceded by a gastrointestinal or respiratory infection within three months prior. (*Id.*; Allan Ropper et al., *Guillain-Barre Syndrome (Landry-Guillain-Barre-Strohl Syndrome, Acute Inflammatory Demyelinating*

Polyneuropathy, AIDP), In: Adams and Victor's Principles of Neurology, 10th Ed. MCGRAW-HILL 1322 (2014) (Ex. 21)).) *Campylobacter jejuni* ("c. jejuni"), cytomegalovirus (CMV), Epstein-Barr virus, and *Mycoplasma pneumoniae* are known precipitants of GBS. (Ropper et al., *supra*, at Ex. 21.) The infection most strongly associated with GBS is *c. jejuni*. (*Id.*) There is also an extensive history of prior cases in this program involving allegations that GBS was caused by vaccination, especially, but not limited to, the flu vaccine.

A small but significant increase in the number of GBS cases post-vaccination was observed with the 1976 swine influenza vaccine. (Baxter et al., *supra*, at Ex. II, pp. 1-2.) An association was again later detected following the 2009 H1N1 monovalent influenza vaccines in the United States. (*Id.*) These causal associations prompted the 2017 addition of GBS to the Vaccine Injury Table relative to the flu vaccine, though it is not included for either the Tdap or meningococcal at issue in this case. National Vaccine Injury Compensation Program: Revisions to the Vaccine Injury Table, 82 Fed. Reg. 6294-01 (Jan. 19, 2017); *see also* 42 C.F.R. 100.3(a). Accordingly, unlike cases involving the flu vaccine, petitioner must meet the above-discussed "causation-in-fact" standard without the benefit of any causal presumption.

Although the flu vaccine stands alone as being presumed to cause GBS within this Program, cases have also concluded that some vaccines other than the flu vaccine can cause GBS. *Salmins v. Sec'y of Health & Human Servs.*, No. 11-140V, 2014 WL 1569478, at *14 (Fed. Cl. Spec. Mstr. Mar. 31, 2014) (accepting an expert opinion that the HPV vaccine (Gardasil) "can cause" GBS although there was no published medical literature demonstrating homology); *Peugh v. Sec'y of Health and Human Servs.*, No. 99-38V, 2007 WL 1531666 (Fed. Cl. Spec. Mstr. May 8, 2007) (finding that the hepatitis B vaccine caused GBS);[4] *Koller v. Sec'y of Health & Human Servs.*, No. 16-439V, 2021 WL 5027947 (Fed. Cl. Spec. Mstr. Oct. 8, 2021) (finding that the pneumococcal vaccine can cause GBS).[5]

[4] On October 13-14, 2004, former Special Master Sweeney held a hearing—which became known as the "Hepatitis B – Neurological Demyelinating Omnibus Proceeding"—to determine whether a causal association exists between the Hepatitis B vaccine and several demyelinating illnesses (multiple sclerosis, TM, chronic inflammatory demyelinating polyneuropathy, and GBS) alleged in four paradigm cases. *Stevens v. Sec'y of Health & Human Servs.*, No. 99-594V, 2006 WL 659525 (Fed. Cl. Spec. Mstr. Feb. 24, 2006); *Werderitsh v. Sec'y of Dept. of Health & Human Servs.*, No. 99-310V, 2006 WL 1672884 (Fed. Cl. Spec. Mstr. May 26, 2006); *Peugh*, 2007 WL 1531666; *Gilbert v. Sec'y of Dept. of Health & Human Servs.*, No. 04-455V, 2006 WL 1006612 (Fed. Cl. Spec. Mstr. Mar. 30, 2006). These cases were then reassigned to former Special Master Laura Millman, who found that in all four cases, the Hepatitis B vaccine was causal. *Peugh*, 2007 WL 1006612, at *1, *17-18.

[5] *See also Pierson v. Sec'y of Health & Human Servs*., No. 17-1136, 2022 WL 322836 (Fed. Cl. Spec. Mstr. Jan. 19, 2022); *Gross v. Sec'y of Health & Human Servs.*, No. 17-1075V, 2022 WL 9669651 (Fed. Cl. Spec. Mstr. Sept. 22, 2022); *Maloney v. Sec'y of Health & Human Servs.*, No. 19-1713V, 2022 WL 1074087 (Fed. Cl. Spec. Mstr. Mar. 17, 2022). *But see Deshler v. Sec'y of Health & Human Servs.*, No. 16-1070V, 2020 WL 4593162 at *21 (Fed. Cl. Spec. Mstr. July 1, 2020); *Bielak v. Sec'y of Health & Humas Servs.*, No. 18-761V, 2023 WL 35509 (Fed. Cl. Spec. Mstr. Jan. 3, 2023).

Notable to this case, however, there are conflicting decisions regarding whether the Tdap vaccine can cause GBS. These decisions have been informed at least in part by how this potential causal relationship has been viewed by the Institute of Medicine ("IOM") in two separate reports, both of which have been filed into the record of this case by respondent. The Institute of Medicine (known as the National Academy of Medicine since 2015) is the medical arm of the National Academy of Sciences. The National Academy of Sciences ("NAS") was created by Congress in 1863 to be an advisor to the federal government on scientific and technical matters (*see* An Act to Incorporate the National Academy of Sciences, ch. 111, 12 Stat. 806 (1863)), and the Institute of Medicine is an offshoot of the NAS established in 1970 to provide advice concerning medical issues. When Congress enacted the Vaccine Act in 1986, it directed that the IOM conduct studies concerning potential causal relationships between vaccines and illnesses. *See* § 300aa-1 note. Special masters have previously observed that the IOM employs a standard for finding causation that is higher than what is required by petitioner's burden of proof. *E.g.*, *Raymo v. Sec'y of Health & Human Servs.*, No. 11-654V, 2014 WL 1092274, at *21 n.39 (Fed. Cl. Spec. Mstr. Feb. 24, 2014). Accordingly, IOM reports and findings are typically approached with caution and generally not treated as dispositive. *Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1252 (Fed. Cir. 2011) (noting the special master's comment that "IOM reports are favored, although not dispositive, in the Vaccine Act Program," then affirming special master's decision). However, numerous prior cases have demonstrated that special masters may account for IOM findings in reaching their decisions.[6]

In 1994, the IOM published a report indicating that "[t]here is biologic plausibility for a causal relation between vaccines and demyelinating disorders." (Kathleen Stratton et al., Committee to Review Adverse Effects of Vaccines, Institute of Medicine, eds.,

[6] *See*, *e.g.*, *Crutchfield v. Sec'y Health & Human Servs.*, 125 Fed. Cl. 251, 262 (2014) (noting that "it was appropriate for the special master to consider the medical literature presented, including the IOM report" and that "the court often has relied on the findings of the Institute of Medicine"); *see also Isaac v. Sec'y Health & Human Servs.*, 108 Fed. Cl. 743, 755 (2013), *aff'd,* 540 Fed. App'x 999 (Mem.) (Fed. Cir. 2013) (affirming the special master's reliance on findings of the IOM); *Cedillo v. Sec'y Health & Human Servs.*, No. 98-916V, 2010 WL 331968, at *94 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *mot. for rev. denied*, 89 Fed. Cl. 158 (2009) (affirming the special master's reliance on conclusions of IOM), *aff'd*, 617 F.3d 1328 (Fed. Cir. 2010); *Rodriguez v. Sec'y Health & Human Servs.*, 67 Fed. Cl. 409, 410 (2005) (relying on an IOM report regarding vaccine causation of an injury); *Althen v. Sec'y Health & Human Servs.*, No. 00-170V, 2003 WL 21439669, at *11 n.28 (Fed. Cl. Spec. Mstr. June 3, 2003) ("Due to the IOM's statutory charge, the scope of its review, and the cross-section of experts making up the committee reviewing the adverse events associated with vaccines, the court considers their determinations authoritative and subject to great deference."), *rev'd on other grounds*, 58 Fed. Cl. 270, 272-74 (2003) (citing IOM reports frequently in support of various scientific propositions), *aff'd*, 418 F.3d 1274 (Fed. Cir. 2005); *Terran v. Sec'y Health & Human Servs.*, 41 Fed. Cl. 330, 337 (1998) (affirming the special master's reliance on conclusions of IOM), *aff'd*, 195 F.3d 1302 (Fed. Cir.1999), *cert. denied*, 531 U.S. 812 (2000); *Cucuras v. Sec'y Health & Human Servs.*, 993 F.2d 1525, 1529 (Fed. Cir. 1993) (noting that the special master had placed "a great deal of weight" on an IOM report in reaching a decision, then affirming the special master's decision); *Stroud v. Sec'y Health & Human Servs.*, 113 F.3d 1258 (Fed. Cir. 1997) (unpublished) (special master may rely upon an IOM report that neither party filed as evidence); *Ultimo v. Sec'y Health & Human Servs.*, 28 Fed. Cl. 148, 152 (1993) (proper for a special master to rely on IOM report).

Adverse Effects of Vaccines: Evidence and Causality, Washington (DC): National Academies Press, p. 106 (1994) (Ex. G) (hereinafter "1994 IOM Report").) Furthermore, the report concluded that the evidence favors a causal relationship between tetanus-containing vaccines and GBS. (*Id.* at 89.) The report indicated that in addition to the biologic plausibility of vaccine-caused demyelination, this conclusion was based on case reports, the most convincing of which was one by Pollard and Selby that demonstrated challenge-rechallenge.[7] (*Id*.) Petitioner, in turn, has filed the Pollard and Selby paper into this record. (*See* J.D. Pollard & G. Selby, *Relapsing Neuropathy Due to Tetanus Toxoid*, 37 J. NEUROL. SCI. 113 (1978) (Ex. 33).) Subsequent cases alleging GBS caused by tetanus vaccines generally found in petitioner's favor.[8]

In 2012, however, the IOM issued a report that revisited this question. (Kathleen Stratton et al., Committee to Review Adverse Effects of Vaccines, Institute of Medicine, eds., *Adverse Effects of Vaccines: Evidence and Causality,* Washington (DC): National Academies Press, p. 588 (2012) (Ex. E) (hereinafter "2012 IOM Report").) The IOM concluded in the 2012 report that the evidence was insufficient to accept or reject a causal relationship between tetanus-containing vaccines and GBS. (*Id*.) This report discussed the Pollard and Selby case report in the context of CIDP and was newly critical of that report and other case reports for failing to adequately rule out alternative causes. (*Id*. at 589-90.) Following this 2012 report, petitioners alleging GBS caused by the tetanus vaccine saw mixed results in this program, with reasoned decisions tending to reject causation, but many cases still compensated by stipulation (and thereby not ultimately reaching the question of causation).[9] However, a more recent decision by another special master examined this history in greater detail, along with additional

[7] The Federal Circuit has noted that "rechallenge" has been "recognized as a form of causation evidence." *James-Cornelius v. Sec'y of Health & Human Servs.*, 984 F.3d 1374, 1380 (Fed. Cir. 2021) (citing *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1322 (Fed. Cir. 2006)). In *Capizzano*, the Federal Circuit explained that "[a] rechallenge event occurs when a patient who had an adverse reaction to a vaccine suffers worsened symptoms after an additional injection of the vaccine. The chief special master stated that this evidence of rechallenge constituted 'such strong proof of causality that it is unnecessary to determine the mechanism of cause—it is understood to be occurring.'" *Capizzano*, 440 F.3d at 1322.

[8] *See Garcia v. Sec'y of Health & Human Servs*., No. 05-720V, 2008 WL 5068934 (Fed. Cl. Spec. Mstr. Nov. 12, 2008) (finding entitlement for petitioner's claim that a Td vaccination caused his GBS); *Watson v. Sec'y of Health & Human Servs.*, No. 96-539V, 2001 WL 1682537 (Fed. Cl. Spec. Mstr. Dec. 18, 2001) (ruling petitioner's GBS was caused by the tetanus vaccine); *Domeny v. Sec'y of Health & Human Servs.*, No. 94-1086V, 1999 WL 199059, at *41 (stating "the possibility that tetanus vaccine can cause GBS is not an issue here because the court accepts that it can"). *But see Tyson v. Sec'y of Health & Human Servs.*, No. 90-3379, 1999 WL 702562 (Fed. Cl. Spec. Mstr. Sept. 30, 1997) (finding against entitlement because preponderant evidence did not support petitioner's claim that a tetanus toxoid-containing vaccine caused his GBS).

[9] *See Isaac v. Sec'y of Health & Human Servs*., No. 08-601V, 2012 WL 3609993 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. rev. denied*, 108 Fed Cl. 743 (2013), *aff'd per curiam*, 540 Fed. App'x 999 (Fed. Cir. 2013); *Tompkins v. Sec'y of Health & Human Servs.*, No. 10-261V, 2013 WL 3498652 (Fed. Cl. Spec. Mstr. June 21, 2013), *mot. rev. denied*, 117 Fed Cl. (2014); *Rupert v. Sec'y of Health & Human Servs*., No. 10-160V, 2014 WL 785256 (Fed. Cl. Spec. Mstr. Feb. 3, 2014). *But see Mohamad v. Sec'y of Health & Human Servs.*, No. 16-1075V, 2022 WL 711604 (Fed. Cl. Spec. Mstr. Jan. 27, 2022).

history regarding other relevant government statements on the subject, and found the petitioner entitled to compensation for post-Tdap vaccine GBS.[10] *Mohamad v. Sec'y of Health & Human Servs.*, No. 16-1075V, 2022 WL 711604 (Fed. Cl. Spec. Mstr. Jan. 27, 2022).

There are far fewer prior cases addressing whether the meningococcal vaccine can cause GBS. In *Whitener v. Secretary of Health & Human Services*, a special master found that the petitioner offered a plausible medical theory for how the meningococcal vaccine can cause GBS. No. 06-0477V, 2009 WL 3007380, at *20 (Fed. Cl. Spec. Mstr. Sept. 2, 2009). Petitioner offered a 2005 CDC Morbidity and Mortality Weekly Report ("MMWR") dispatch health alert reporting five cases of GBS following the meningococcal vaccine. *Id.* at 8, n.17. (An updated 2006 MMWR regarding the same topic was filed by the petitioner in this case as Exhibit 17.) Although the special master noted that there was no epidemiological evidence to support causation, he found that the CDC's MMWR dispatch article demonstrated at least an incidental association. *Id.* at 20. Petitioner also relied on the 1994 IOM report's description of GBS as an immune-mediated disease to support the theory of causation. *Id.* Given that petitioner suffered from an immune mediated autoimmune demyelinating disease and that the MMWR dispatch "implicate[d] the meningococcal vaccine as one vaccine for which this mechanism appears plausible," the special master concluded that petitioner offered preponderant evidence that the meningococcal vaccine can cause GBS. *Id.* In a subsequent case, however, a different special master examined the same underlying case reports and reached the opposite conclusion.[11] *Tompkins v.*

[10] In addition to the IOM reports discussed above, the *Mohamad* case also involved discussion of recommendations by the Advisory Committee on Immunization Practices ("ACIP"), which is made up of members selected by the Secretary of Health and Human Services to advise the Director of the Centers for Disease Control, and testimony further expounding on the ACIP's activities. *Mohamad*, 2022 WL 711604, at *9-10, 15-16. Relevant to the analysis in *Mohamad*, the ACIP issued a recommendation in 1996 that purported to find some "extremely low" risk for GBS following tetanus vaccination. (*Id*. at 11.) Additionally, the ACIP issued additional recommendations in 2011, 2018, and 2019 that included a precaution against tetanus vaccination for those who previously suffered GBS within six weeks of a prior tetanus-containing vaccination. (*Id*. at 12, 14-15.) Considering the whole history of reports and actions taken under the authority of the Secretary of Health and Human Services, the special master concluded that the government's acknowledgement of a post-vaccination risk satisfied petitioner's burden of proof. (*Id*. at 17-18.) Apart from the previously referenced IOM reports, none of these materials have been filed into the record of this case.

[11] In *Tompkins*, the special master indicated that what the petitioner in that case had relied upon was only a "news release from the U.S. Food & Drug Administration dated September 30, 2005" that included five case reports. 2013 WL 3498652, at *26. However, in the earlier *Whitener* case, the special master explained that petitioner's expert in that case, Dr. Kinsbourne, had explained that the five case reports were originally discussed in the September 30, 2005 FDA Health Alert, but that the same case reports were addressed again in a later MMWR dispatch dated October 6, 2005. 2009 WL 3007380, at n.17. Petitioner in that case relied specifically on the MMWR. According to the CDC's website, the MMWR is "the agency's primary vehicle for scientific publication of timely, reliable, authoritative, accurate, objective, and useful public health information and recommendations." *See About the Morbidity and Mortality Weekly Report (MMWR) Series*, CDC.GOV, www.cdc.gov/mmwr/about.html (last accessed Feb. 16, 2023). Thus, for example, in *Mohamad,* 2022 WL 711604, the special master explained that the MMWR is the vehicle through which the ACIP recommendations discussed in n.10, *supra*, are publicized as "official CDC/HHS recommendations to the general public." 2022 WL 711604, at *10.

Sec'y of Health & Human Servs., No. 10-261V, 2013 WL 3498652, at *26 (Fed. Cl. Spec. Mstr. June 21, 2013).

III. Procedural History

As noted above, the petition was filed in this case on June 29, 2018. (ECF No. 1.) Initially it was assigned to Special Master Sanders. (ECF No. 4.) From that point until September of 2018, petitioner filed medical records and affidavits marked as Exhibits 1-14. (ECF Nos. 8-9, 12-14.) On September 27, 2018, petitioner filed an amended petition specifying that Cameron suffered from the Miller Fisher variant of GBS. (ECF No. 16.)

Respondent filed his responsive Rule 4 Report on March 25, 2019. (ECF No. 22.) In his report, respondent acknowledged that several of petitioner's treating physicians attributed his GBS to his vaccinations, but raised two primary issues. First, absent a causal presumption, petitioner could not establish that the vaccines at issue in this case "can cause" GBS without an expert opinion. (*Id*. at 10.) Second, respondent contended that the interval of onset of petitioner's GBS was "too short" relative to vaccination to be medically reasonable, contending that onset occurred less than 24 hours post-vaccination. (*Id*. at 11-12.) Respondent contended that the treating physician opinions were limited to recognizing the coincident timing. (*Id*. at 10-11.)

Following the filing of respondent's report, petitioner filed an expert report by neurologist Yuval Shafrir, M.D. (ECF No. 29; Ex. 15.) The report was accompanied by a curriculum vitae (Ex. 16) and medical literature marked as Exhibits 17-64. (ECF Nos. 29-33.) Included within Dr. Shafrir's assessment was a contention that onset of GBS should be identified based on weakness, which occurred two days post-vaccination. (Ex. 15, pp. 29, 35.)

Shortly thereafter, the case was reassigned to my docket on August 29, 2019. (ECF No. 36.) In a scheduling order issued September 24, 2019, I noted Dr. Shafrir's assessment of onset and observed that, contrary to respondent's specific contention, it appeared from the medical records that onset of numbness, tingling, and facial droop, occurred just outside of 24 hours post-vaccination. (ECF No. 37.) I encouraged the parties to consider litigative risk settlement. (*Id*.) Petitioner provided a demand to respondent; however, respondent opted to file responsive expert reports rather than commence settlement discussions. (ECF Nos. 37, 39-40.)

On January 6, 2020, respondent filed expert reports by neurologist Leslie Benson, M.D. (Ex. A (with curriculum vitae as Ex. B)) and immunologist Craig Platt, M.D., Ph.D. (Ex. C (with curriculum vitae as Ex. D)). (ECF No. 41.) Respondent filed accompanying medical literature marked as Exhibits E-QQ. (ECF No. 42.) In response, petitioner filed an expert report by immunologist Omid Akbari, Ph.D., marked as Exhibit 65 along with a curriculum vitae (Ex. 66) and accompanying medical literature marked as Exhibits 67-119. (ECF Nos. 47-52.) Respondent filed a supplemental report by Dr.

Platt responding to Dr. Akbari's report along with two additional supporting citations. (ECF No. 55; Exs. RR-TT.)

Subsequently, in a status report filed February 22, 2021, petitioner indicated that Dr. Platt's supplemental report did not raise any novel issues and therefore petitioner did not intend to file any further supplemental expert reports. (ECF No. 56.) A follow up status conference was held on May 5, 2021, to discuss how the case would proceed. (ECF No. 60.) Petitioner then opted to proceed with a ruling on the written record in lieu of scheduling an entitlement hearing. (ECF No. 65.) However, having reached that conclusion, petitioner requested an opportunity to file supplemental expert reports to address issues that would otherwise have been addressed by oral testimony. (*Id*.)

On September 16, 2021, petitioner filed a supplemental report by Dr. Akbari marked as Exhibit 120 and accompanying literature marked as Exhibits 121-134b. (ECF Nos. 67-68.) Respondent filed a responsive report by Dr. Platt with one additional citation. (ECF No. 71; Exs. UU-VV.) Petitioner filed her motion for a ruling on the written record on February 9, 2022. (ECF No. 74.) Respondent filed a response on April 18, 2022. (ECF No. 76.) Petitioner filed her reply on May 3, 2022. (ECF No. 77.)

I have determined that the parties have had a full and fair opportunity to present their cases and that it is appropriate to resolve this issue without a hearing. *See* Vaccine Rule 8(d); Vaccine Rule 3(b)(2); *Kreizenbeck v. Sec'y of Health & Human Servs*., 945 F.3d 1362, 1366 (Fed. Cir. 2020) (noting that "special masters must determine that the record is comprehensive and fully developed before ruling on the record"). Additionally, during the May 5, 2021, status conference I confirmed that neither party objected to proceeding to a decision on the written record. (ECF No. 60.) Accordingly, this matter is now ripe for resolution.

IV. Party Briefs and Issues to Be Decided

In his motion for a ruling on the written record, petitioner stresses that there is no debate in this case as to his GBS diagnosis. (ECF No. 74, pp. 33-34.) He further contends that he has satisfied the three *Althen* prongs in order to demonstrate that his GBS was caused by his July 8, 2015 vaccinations. (*Id.* at 31.)

Petitioner relies on his experts' opinions with respect to *Althen* prong one's requirement of a medical theory of causation. (*Id*. at 34-44.) He stresses that the pathogenesis of GBS is multifactorial and that vaccination is among the "well-known" triggers of GBS. (*Id*. at 34-35.) Petitioner's arguments with respect to *Althen* prong one span several lines of evidence discussed further below. (*Id*. at 34-44.)

With regard to *Althen* prong two (a logical sequence of cause and effect), petitioner stresses notations by his treating physicians accepting a causal relationship between his GBS and his vaccinations and seeming to discount the possibility that the GBS was related to a positive streptococcal culture. (ECF No. 74, pp. 44-51.)

Petitioner further contends that the vaccinations would remain a substantial contributing factor to his GBS even if infection additionally played a role. (*Id*. at 49-51.)

Regarding *Althen* prong three (an appropriate temporal relationship), petitioner argues that onset of his GBS, as evidenced by numbness and tingling, occurred *more than* 24 hours post-vaccination, which therefore constitutes "day 2" in the relevant literature. (*Id*. at 51.) Petitioner cites several pieces of literature that he contends support a causal relationship based on this onset. (*Id*. at 51-54.) Further to this, petitioner explains that his experts have set forth mechanistic evidence indicating, based on immunological memory and cytokine response, why the rapid onset seen in this case is appropriate. (*Id*. at 54-55.)

Finally, petitioner contends that respondent has not met his burden of establishing that petitioner's GBS was caused by a factor unrelated to vaccination, namely a streptococcal infection. (ECF No. 74, pp. 55-57.)

In response, respondent argues that petitioner has failed to preponderantly establish any of the three *Althen* prongs. (ECF No. 76.)

Regarding *Althen* prong one, respondent contends that petitioner's experts' opinions are unreliable, stressing that these opinions mostly rely on case reports (entitled to little weight) whereas larger epidemiologic studies do not support causation. Respondent further charges that petitioner's experts are misleadingly relying on an outdated IOM report (the 1994 report) and haven't substantiated the molecular mimicry they theorize. (*Id*. at 12-14.)

Regarding *Althen* prong two, respondent contends that there can be no logical sequence of cause-and-effect implicating petitioner's vaccinations, both because the timing of onset is too short and because an infectious cause was not ruled out. (*Id*. at 14-15.)

With respect to *Althen* prong three, respondent asserts that onset of petitioner's GBS occurred *less than* 24 hours after his vaccinations based on a competing assessment of the onset of numbness and tingling. (*Id*. at 16.) Respondent contends this is "not long enough for the manifestation of a systemic autoimmune response, particularly where the response allegedly involves molecular mimicry and autoantibody production." (*Id.*)

Respondent offered no assertion that he had met his burden of proof with respect to establishing any factor unrelated to vaccination as the cause of petitioner's GBS.

Petitioner filed a reply disputing respondent's assessment of the timeline of onset. (ECF No. 77.) Petitioner also resisted respondent's contention that her experts had misleadingly relied on the earlier IOM report. (*Id*.)

V. Factual Summary

a. Vaccination and First Emergency Department Presentation

Petitioner was born on December 9, 2003. (Ex. 2, p. 2.) Prior to the subject vaccinations, the parties agree that petitioner was a healthy child with no history of neurological issues or chronic health concerns. (ECF No. 74, p. 3; ECF No. 76, p. 2.)

On July 8, 2015, petitioner saw Dr. Matthew Penson, his primary care physician, for a routine physical. (Ex. 2, pp. 61-62.) At the time of his appointment, petitioner was approximately eleven and a half years old. (*Id.*) The record of examination reflects normal results and no significant concerns. (*Id.*) During this visit, petitioner received the subject Tdap and meningococcal vaccines.[12] (*Id.*) In her affidavit, petitioner's mother recalls:

> The next day, July 9, 2015, I picked up [petitioner] from camp. When we got home, [petitioner] had something to eat and then said that he wanted to lie down. I asked him how he was feeling, and he said that he was tired and that his left arm was sore from the vaccines he received the day before. [Petitioner] napped for three hours on July 9, 2015, which was unusual for him. When he woke up, I asked him to open his eyes and he said that they were open, however, they were not. I waited for him to fully wake up, but after a few minutes, I noticed that his left eye was partially closed. [Petitioner] said that he did not feel very well and was extremely tired. I felt uneasy, so I decided to take him to the ER . . . .

(Ex. 13, pp. 1-2.)

Petitioner presented to the Emergency Department ("ED") at Joe DiMaggio Children's Hospital around 10:30 PM. (Ex. 4, pp. 5-8.) Petitioner's mother reported that he had received the Tdap and meningococcal vaccines the previous day, and "[s]hortly after, he began having mild pain [in the] area of his arm where he received the vaccine." (*Id.* at 5.) She gave him ibuprofen for the pain and sent him to band camp for the day. (*Id.*) When she picked him up from camp, he complained that his arm pain had returned, so she gave him another dose of ibuprofen around 4:00 PM and he went to sleep. (*Id.*) When he later awoke on July 9, 2015, she noticed that his left eyelid appeared to be drooping, and he complained of tingling and numbness in his fingertips bilaterally, extending to his wrists, and in his toes, extending to both feet. (*Id.*) Due to cramping in his feet, he was unable to walk, and had to crawl toward his room. (*Id.*) He also had the sensation that his feet were cold. (*Id.*) At the ED, his pain had resolved, and he could walk normally, although the paresthesia persisted. (*Id.*)

[12] Although several records indicate that petitioner received a "DTaP" vaccine, according to petitioner's vaccination record he received "Tdap" (Adacel) and Meningococcal MCV4P (Menactra) vaccines on July 8, 2015. (Ex. 1, p. 2.)

A physical examination was notable for left ptosis, but was otherwise normal, with 5/5 strength, normal tone, intact sensation, and normal gait; reflexes were not documented. (Ex. 4, p. 7.) A brain CT scan was unrevealing. (*Id.* at 17.) By around midnight on July 9, 2015, the numbness and tingling had slightly improved, and he was discharged home in the early morning hours of July 10, 2015, with diagnoses of ptosis of the left eyelid and possible immunization reaction. (*Id.* at 7-8.)

b. Inpatient Hospitalization July 10 – July 27, 2015

On July 10, 2015, petitioner returned to the ER complaining of persistent pain in his hands and the left side of his arm, and a burning sensation in his hands and feet. (Ex. 4, pp. 33-39.) On examination, his ptosis was not visible, and he was able to stand without difficulty but only after multiple distractions, due to his distress.[13] (*Id.* at 35, 38.) He also was uncooperative with the measurement of extremity strength and the elicitation of reflexes. (*Id.* at 38.) The ER physician ordered a lab work-up and MRI studies, and consulted with several specialists, including those in neurology and infectious disease. (*Id.* at 38-39.) The infectious disease specialist indicated that GBS was not associated with the meningococcal vaccine. (*Id.* at 39.) The neurologist admitted petitioner for a full evaluation. (*Id.*)

Following admission, petitioner experienced worsening weakness, with loss of reflexes, dysarthria, and ophthalmoplegia. (Ex. 4, pp. 42, 1819.) On July 11th, he was placed in the IMCU for observation. (*Id.* at 49.) MRIs of the brain and spine were negative. (*Id.* at 52-53.) An infectious disease consult noted that petitioner had been camping in North Carolina for one week in June and then spent time with his grandmother, where he swam and waterskied at a lake. (*Id.* at 58.) An examination was notable for lateral third cranial nerve (oculomotor nerve) weakness, upper extremity weakness, difficulty obtaining reflexes, and ataxia on the nose-to-finger test. (*Id.* at 59.) Complete blood count ("CBC"), metabolic panel, and creatine phosphokinase ("CPK") were normal. (*Id.* at 60-61.) A lumbar puncture was performed and showed normal indices. (*Id.* at 65.) The assessment was rule out Miller-Fisher variant of GBS, early signs of amoebic encephalitis, or another neurologic condition. (*Id.* at 62.) Petitioner began a four-day course of IVIG. (*Id.* at 66.)

On July 13, 2015, petitioner's condition had worsened, "with acute ascending neuromuscular weakness likely GBS. Now committed to BiPAP, with neuromuscular weakness that is progressing as expected. Expect will need mechanical ventilation." (Ex. 4, p. 107.) That same day, an immunologist asked for further details of petitioner's vacations prior to onset of his illness, including where he stayed and what he did during those times. (*Id.* at 67.) On examination, petitioner was unable to speak, but could follow commands. (*Id.* at 68.) He had bilateral ptosis and could not abduct his right eye. (*Id.*) He was areflexic. (*Id.*) The impression was GBS. (*Id.* at 70.)

[13] The medical records indicate that petitioner was in moderate distress, intermittently agitated, and crying. (Ex. 4, pp. 37-38.)

Also on July 13, 2015, Dr. Matthew Penson submitted a report to the Vaccine Adverse Event Reporting System ("VAERS"). (Ex. 9, pp. 1-2.) That same day Dr. Martinez assessed petitioner with an "atypical case of GBS in view of symptoms and [history] of vaccine in spite of labs[.] [Patient] has developed increasing weakness[,] loss of [deep tendon reflexes,] and evidence of cranial nerve involvement . . . [Rule out] infectious process or side effect secondary to vaccine[.] [Patient] was exposed to bats[.]" (Ex. 4, pp. 108-11.) Dr. Martinez canceled NMDA testing as "this does not appear[] to be NMDA encephalitis and add[ed] Enterovirus PCR to csf and West Nile virus PCR[.]" (*Id.*) Dr. Martinez planned to repeat MRI of the brain and spine and ordered an ophthalmology consult. (*Id.*)

That same day, ophthalmologist Marien Leon, M.D., assessed petitioner with GBS, with opthalmoparesis, possible Miller Fisher variant. (Ex. 4, p. 72.) Petitioner's exam findings were "suggestive of at least mild ophthalmoparesis. As his limitation in abduction was worse [in both eyes] than in any other direction, conditions which cause bilateral 6th nerve palsies such as Miller Fisher and increased intracranial pressure should also be considered." (*Id.*)

On July 14, 2015, petitioner was intubated for respiratory failure with progressive ascending weakness. (Ex. 4, p. 76.) Nerve conduction velocity ("NCV") studies were also done, with abnormal results in all nerves tested. (Ex. 11, pp. 1-4.) The findings were consistent with a sensorimotor polyneuropathy with both axonal and demyelinating features. (*Id.* at 2.) The presence of conduction blocks and temporal dispersion were consistent with a diagnosis of acute inflammatory demyelinating polyneuropathy ("AIDP"). (*Id.*)

On July 15, 2015, repeat brain and spine imaging revealed small T2 hyperintense focus in the right frontal white matter not visible on prior MRI. (Ex. 4, p. 75.) It was thought to be nonspecific, "but may represent a small focus of demyelination. No abnormal enhancement is seen." (*Id.*) The spine MRI revealed mild enhancement of the cauda equina roots in the lumbar regions, "that is either increased or new in comparison with 7/10/15, and that is compatible with a given clinical diagnosis of Guillain-Barre Syndrome." (*Id.* at 619.) Petitioner had a positive throat swab for streptococcus ("strep"). (*Id.* at 158.)

On July 17, 2015, a neurology consult noted that petitioner was still intubated, but his strength was improving slightly. (Ex. 4, p. 75.) He still had impaired eye movement and areflexia. (*Id.*) Mild enhancement of the nerve root was noted in the lumbar area on the MRI with contrast, and NCV studies showed both demyelinating and axonal injury of the peripheral nerves. (*Id.*) The infectious work-up was negative to date. (*Id.*) Neurology questioned whether a strep infection, which he apparently had prior to this illness (and which his sister had shortly before he did) "may be the causative factor in triggering this illness rather than viral infections or the immunization he received before the illness occurred." (*Id.*) An immunology consult suspected vaccine associated atypical GBS, but similarly noted the positive strep as a possible contributing factor in the development of GBS. (*Id.* at 200.)

On July 22, 2015, petitioner was extubated. (Ex. 4, pp. 266-68.) At this point, petitioner had bilateral ptosis, right greater than left. (*Id.* at 266.) He could shrug his shoulder, had 3+/5 strength in the upper extremities and 2/5 in the lower extremities, could move his toes and his hands to midline and upwards, and had 2+ reflexes. (*Id.*) On July 23, 2015, petitioner was transferred out of the ICU. (*Id.* at 284-85.) All viral and bacterial cultures remained negative, except for evidence of strep throat. (*Id.*) The latest imaging results were consistent with GBS, and "an IgG GM 1 antibody positive [was] also indicative of peripheral neuropathic disease. Per immunology and infectious disease, process is likely related to the Menactra vaccination the child received approximately a week ago [*sic*]. Report has been made to the vaccine adverse event system." (*Id.*)

On July 27, 2015, petitioner was discharged to rehabilitation. (Ex. 4, pp. 41-44.) Discharge diagnoses included GBS "following vaccination," respiratory failure, paresthesia, dysesthesia, and Miller Fisher variant GBS. (*Id.* at 42.) Over the course of petitioner's hospitalization his throat culture was positive for Group A Strep and he received a course of Clindamycin; completed a course of Doxycycline to cover for tick-born pathogens; and his viral and bacterial cultures including CSF were all negative. (*Id.* at 43.)

c. Inpatient Rehabilitation July 27 – August 14, 2015

On July 27, 2015, petitioner began inpatient rehabilitation, with physical, occupational, and speech therapies. (Ex. 4, pp. 1815-18.) He was admitted with weakness, deficits in mobility and activities of daily living ("ADLs"), and dysesthetic pain. (*Id.*) At discharge on August 14, 2015, petitioner was independent with ADLs and was walking both with and without a walker, with mild gait deviations. (Ex. 4, pp. 1816-17.) He could navigate stairs with a railing and did not need to wear his ankle-foot orthotics. (*Id.*) He was able to eat and drink without difficulty. (*Id.*) His discharge examination was notable for mild right ptosis, tight hamstrings, and gait abnormality. (*Id.*) His strength was generally improved, but he had ongoing core weakness. (*Id.*) He was to receive physical therapy three times per week and occupational therapy twice per week. (*Id.*)

d. Treatment Following Discharge from Inpatient Rehabilitation

On August 28, 2015, petitioner had his first rehabilitation follow-up. (Ex. 6, pp. 35-45.) His strength was mostly 5/5, with some decrease in the upper extremities, but he continued to improve. (*Id.* at 41.) At a neurology follow-up on October 5, 2015, petitioner was doing well, but reported tiring easily, especially in the mornings in school. (Ex. 5, pp. 139-40.) He was still receiving physical and occupational therapy. (*Id.*) He continued to have burning pain in his arms and ankles, for which he was taking medication as needed. (*Id.*) On examination, he had normal cranial nerves, and normal muscle tone and extremity strength, but his deep tendon reflexes were diffusely absent. (*Id.*) Petitioner's gait and balance were normal, with the ability to stand on one leg and hop. (*Id.*)

At an October 28, 2015 rehabilitation follow-up, petitioner reportedly was less tired, but he still required rest during the school day. (Ex. 6, pp. 153-58.) He had no sensory deficits and had normal muscle tone and normal coordination. (*Id.*) He had diminished heel strike on the left, intermittently, but continued to improve overall. (*Id.*) petitioner was discharged from occupational therapy on October 30, 2015. (Ex. 8, pp. 1054-58.) He had met all his short-term goals and 75-100 percent of his long-term goals. (*Id.* at 1057.) He was to work on overall endurance and upper extremity strength and independence. (*Id.* at 1058.) On November 18, 2015, petitioner saw Dr. Penson, who noted that his GBS and symptoms were improving, although he still had mild decreased reflexes. (Ex. 2, pp. 17-20.) Subsequently petitioner returned to the Boy Scouts. (*Id.*)

That same day, petitioner also had a neurology follow-up. (Ex. 7, pp. 106-07.) He was doing well from a motor standpoint but complained of pains in his back and legs at the end of the day. (*Id.*) He also had brief headaches. (*Id.*) However, he had recently walked for over two hours with his family on Halloween, was able to go to the store with his mother without complaints and had gone on some retreats with the Boy Scouts. (*Id.*) He also had been exercising with a bike and receiving physical therapy. (*Id.*) On examination, he had decreased reflexes, but normal sensation. (Ex. 7, p. 107.) His gait was normal, and he could walk and squat without problem; however, he had mild decreased dexterity and difficulty hopping on either leg alone. (*Id.*)

A physical therapy progress note dated December 2, 2015, reflects that petitioner had started playing football in the neighborhood and was cleared to return to school sports. (Ex. 8, p. 1106.) Petitioner still reported pain with intense exercise, and fatigue with long periods of standing or walking. (*Id.*) Petitioner also had gait deviations with longer walks. (*Id.*) He was encouraged to continue physical therapy. (*Id.*) On January 25, 2016, a VAERS report was completed by Sanofi Pasteur, the manufacturer of the vaccines. (Ex. 9, pp. 21-23.) The report concludes that "further information on the confirmation of the diagnosis, patient medical history, as well as etiological infectious work-up for this pathology . . . are needed to further assess this case. Moreover, the patient received two vaccines simultaneously making it difficult to assess the role of each vaccine in particular." (*Id.* at 23.)

Petitioner was discharged from physical therapy on February 3, 2016, nearly seven months after the onset of his GBS. (Ex. 2, pp. 52-57.) On that date he was independent and had met 90 percent of his rehabilitation goals. (*Id.* at 56.) He was discharged to a home exercise program. (*Id.*)

On February 24, 2016, petitioner had a neurology follow-up. (Ex. 2, pp. 45-50.) He reportedly was able to walk, hop, and jump, and run at least a quarter-mile. (*Id.*) He still experienced tiredness and had some "high level balance issues" (e.g., unable to balance on a skateboard or steer his bike as well as he used to). (*Id.*) He denied paresthesia and dysesthesia. (*Id.*) His physical exam was essentially normal, except for hyporeflexia. (*Id.*) On June 7, 2016, petitioner had another neurology follow-up.

(Ex. 7, pp. 128-29.) It was now eleven months after onset of GBS and he had made an excellent recovery. (*Id.*) A detailed examination was normal except for some gross motor incoordination with hopping on either foot alone. (*Id.*) He had intermittent discomfort in his limbs, which he treated with Advil. (*Id.*) His prognosis was good. (*Id.*)

On July 12, 2016, Dr. Penson received a one-year follow-up letter from VAERS asking for information on petitioner's current condition. (Ex. 2, pp. 38-39.) Dr. Penson responded that petitioner had recovered from the adverse event and was "much better, discharged from physical therapy. Still has neuropathies → weaning meds." (*Id.*) On August 15, 2016, petitioner had a twelve-year-old check-up, with no major concerns noted. (Ex. 2, pp. 11-15.) He was doing well, but still had occasional pain. (*Id.*) He had been discharged from neurology. (*Id.*) His physical examination, which included a neurological assessment, was normal. (*Id.* at 12.)

On August 16, 2017, about two years after GBS onset, petitioner had a thirteen-year-old check-up, with no major concerns noted. (Ex. 2, pp. 5-9.) Petitioner was participating in physical activities, and aside from being overweight, his examination was normal, including musculoskeletal and neurological assessments. (*Id.*)

VI. Expert Opinions

a. Petitioner's Neurologist, Yuval Shafrir, M.D.[14]

Petitioner filed one report by neurologist Yuval Shafrir, M.D. (Ex. 15.) Dr. Shafrir notes that petitioner did have some early reaction to vaccination unrelated to GBS in the form of arm soreness and tiredness. (*Id*. at 30.) However, he places onset of the GBS as occurring on July 9, 2015, more than 24 hours post-vaccination. (*Id.*) This timing derives from the onset of weakness that occurred after petitioner's first ER presentation following his ptosis and which led to his hospital admission the next day. Dr. Shafrir opines that petitioner's initial post-vaccination ptosis followed a different clinical trajectory from the other cranial nerve involvement seen as part of his GBS and was more likely a separate cranial nerve palsy than a symptom of his later diagnosed GBS.[15] (*Id.*)

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[14] Dr. Shafrir received his medical degree from the Sackler School of Medicine at Tel Aviv University in 1982. (Ex. 16, p. 1.) He completed his residency in pediatrics at North Shore University Hospital in Manhasset, New York and his pediatric neurology residency and fellowship at the Washington University Medical Center in St. Louis, Missouri. (*Id.*) In 1992 Dr. Shafrir completed his pediatric neurophysiology and epileptology fellowship at Miami Children's Hospital. (*Id.*) He is board certified in neurology with a special qualification in child neurology as well as clinical neurophysiology. (*Id.* at 2.) Dr. Shafrir began his own neurology practice in May 2000, where he currently serves as a pediatric neurologist. (*Id.* at 3.) He currently serves as an assistant professor in the Department of Pediatrics for the University of Maryland School of Medicine in Baltimore Maryland. (*Id.*) He also teaches residents and medical students at Sinai Hospital, Department of Pediatrics. (Ex. 16, p. 3.) Dr. Shafrif has co-authored several publications in various neurology journals, though none on GBS or polyneuropathy specifically. (*See id.* at 3-5.)

[15] Dr. Shafrir explains that ptosis is a form of 3rd cranial nerve palsy. Citing a prior review paper by Woo, et al., he suggests that such isolated nerve palsies have been documented in the Vaccine Adverse

Dr. Shafrir explains that petitioner's presentation was atypical, which initially confused his treating physicians.[16] (Ex. 15, pp. 30-31.) He notes that the treating physicians initially included infectious causes in their differential diagnosis, particularly streptococcal throat infection, but suggests that post-vaccination GBS was the ultimate diagnosis. (*Id*. at 31.) He opines that an infectious etiology is less likely. Given the rapidity of onset, it is very unlikely that any nerve inflammation predated petitioner's vaccinations. Additionally, workup for an infectious etiology was negative except for a strep infection. However, petitioner did not show any signs of strep infection until after being intubated and streptococcal infection is not a common precedent for GBS. (*Id*.)

Dr. Shafrir acknowledges that Vaccine Injury Table includes a three-day minimum latency for GBS caused by the flu vaccine but discusses a number of factors which he suggests may explain the quicker onset in this case. (Ex. 15, pp. 36-37.) First, individual genetic differences may affect both susceptibility and antibody production. (*Id*.) Second, GBS, though generally understood to be an autoimmune condition stemming from the adaptive immune response, also has a cytokine driven innate immune aspect. (*Id*. at 32-33.) For example, Dr. Shafrir cites a meta-analysis of 30 prior studies comprising 1,302 GBS patients and 1,073 health controls. (Ting Sun et al., *Peripheral Blood and Cerebrospinal Fluid Cytokine Levels in Guillain Barre Syndrome: A Systematic Review and Meta-Analysis,* 13 FRONT. NEUROSCI. 1 (2019) (Ex. 47)).) The meta-analysis found that tumor necrosis factor ("TNF") alpha, interleukin ("IL") 1-beta, Il-6, IL-4, IL-17, and interferon gamma, are significantly elevated among GBS patients. (*Id*. at 1.) The authors hypothesize that these findings are pathologic in GBS, noting in particular that prior study has shown T-cell produced TNF-alpha to have a direct myelinotoxic effect on myelinated fibers. (*Id*. at 5-6.) Dr. Shafrir suggests that the AIDP form of GBS that petitioner suffered is more T-cell dependent than the AMAN form of GBS, which is more antibody dependent. (Ex. 15, p. 33.)

Dr. Shafrir suggests that petitioner's own history suggests a number of reasons to believe there was "prominent" activation of post-vaccination cytokines. (Ex. 15, p. 37.) He notes petitioner's initial localized reaction to the vaccination and cites literature indicating that the fifth dose of DTaP immunization has been showed to cause cytokine-

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Events Reporting System ("VAERS") as consequences of vaccination. (Ex. 15, p. 30 (citing Emily Jane Woo et al., *Motor Palsies of Cranial Nerves (Excluding VII) After Vaccination. Reports to the US Vaccine Adverse Event Reporting System,* 10 HUM. VACCINE IMMUNOTHER. 301 (2014) (Ex. 19)).) Dr. Shafrir notes that Woo et al., identified a minimum timing to onset of 0.3 days. (*Id*.) Woo et al., includes cases as far out as 3,285 days (*i.e.,* nine years), but indicates that the median timing of onset was 9 days. (Ex. 19, p. 3.) Thus, Dr. Shfarir opines that petitioner's ptosis may have been an independent consequence of vaccination. (Ex. 15, p. 30.)

[16] Specifically, Dr. Shafrir cites the following unusual factors: earlier prominent involvement of the cranial nerve, presence of anti-GM1 IgG antibodies, presence of white blood cells but no elevated protein in the spinal tap, intact deep tendon reflexes even after onset of weakness and inability to walk, rapid recovery of deep tendon reflexes, severe pain upon initial presentation, and demyelination in the brain. (Ex. 15, pp. 30-31.)

related local reactions more often than earlier doses.[17] (*Id*. (citing Danuta Skowronski et al., *Injection-Site Reactions to Booster Doses of Acellular Pertussis Vaccine: Rate, Severity, and Anticipated Impact,* 112 PEDIATRICS 1 (2003) (Ex. 63)).) Thus, Dr. Shafrir notes for example that in contrast to the three-day latency between the flu vaccine and the peripheral nerve damage seen in GBS, the Vaccine Injury Table includes a lesser 48-hour onset period for brachial neuritis following tetanus vaccine—brachial neuritis being another form of immune mediated peripheral nerve disorder. (*Id*. at 37.) Moreover, petitioner was also simultaneously administered the Menactra vaccine, which is conjugated using the diphtheria toxoid and contains six times as much of the toxoid as typical Td vaccines. Menactra has been shown to be substantially more immunogenic than Td vaccines alone. (Ex. 15, p. 35 (quoting Tejpratap Tiwari & Melinda Wharton, *Diphtheria Toxoid, In: Vaccines,* 6th Ed, Edited by Stanley A. Plotkin et al., ELSEVIER INC., 21 (2012) (Ex. 42)).) Further, petitioner had pain, malaise and fatigue before onset of other signs of GBS, which are very likely cytokine-mediated symptoms.[18] (*Id*. at 37-38.) Dr. Shafrir suggests that the pro-inflammatory cytokines associated with the DTaP vaccine, including IL-6, interferon gamma, and TNF alpha, are also elevated in GBS. (*Id*. at 38.)

Dr. Shafrir indicates that immunizations broadly are "a well-known trigger" for GBS. (Ex. 15, p. 32.) He cites the influenza vaccination as having an established causative relationship and further stresses that "almost every known febrile infection and immunization has at one time or another been reported to precede GBS (some probably coincidental)." (*Id*. (quoting Allan Ropper et al., *Guillain-Barre Syndrome (Landry-Guillain-Barre-Strohl Syndrome, Acute Inflammatory Demyelinating Polyneuropathy, AIDP), In:* Adams and Victor's Principles of Neurology, 10th Ed. MCGRAW-HILL 1322, 1324 (Ex. 21)).) Dr. Shafrir cites two papers for the proposition

[17] The study compared children who received a fifth consecutive dose of acellular pertussis vaccine against those who received a mixed series that include some whole-cell pertussis vaccinations. They reported more injection site reactions in the former group. Petitioner's records show that on July 8, 2015, he received an "Adacel" vaccination. (Ex. 2, p. 3.) Adacel is a Tdap vaccine for ages ten to 64. *See Adacel,* FDA.GOV, www.fda.gov/vaccines-blood-biologics/vaccines/adacel (last accessed Feb. 17, 2023). Petitioner previously received a complete five dose series of "Daptacel" vaccinations on February 10, 2004, April 12, 2004, June 22, 2004, June 16, 2005, and March 13, 2009. (Ex. 2, p. 3.) Daptacel is a diphtheria tetanus and acellular pertussis vaccine given to children between six weeks and 6 years of age. *See Daptacel,* FDA.GOV, www.fda.gov/vaccines-blood-biologics/vaccines/daptacel (last accessed Feb. 17, 2023).

[18] Dr. Shafrir stresses that the pain of GBS in particular has been associated with cytokines. He cites a paper evaluating a previously conducted study. The paper indicates that the underlying article identifies two types of pain associated with GBS, pain starting before onset of weakness that is mainly radicular muscle pain of the extremities and chronic arthralgia of the limbs associated with weakness and disability. (Thirugnanam Umapathi & Nobuhiro Yuki, *Pain in Guillain-Barre Syndrome,* 11 EXPERT REV. NEUROTHER. 335, 338 (2011) (Ex. 64).) Regarding the former, the study hypothesized that "neuropathic pain, where inflamed or damages large myelinated sensory fibers may lead to the dysesthesia, as well as the muscle pain in the extremities. This may explain the correlation of pain with severity of illness at nadir in the acute phase." (*Id.*) Furthermore, "[a]nimal studies have suggested a role for T-cell mediated inflammation and the release of proinflammatory cytokines producing thermal hyperalgesia and allodynia in experimental autoimmune neuritis." (*Id*.)

that about 10% of hospitalized GBS patients had a preceding immunization, noting in particular that a Canadian study of children found tetanus-containing vaccinations to be the most common preceding immunization. Meningococcal vaccine also preceded several cases.[19] (*Id*. (citing Karina Top et al., *Guillain Barre Syndrome After Immunization in Canadian Children (1996-2012),* 34 PEDIATR. INFECT. DIS. J. 1411 (Ex. 23); Joachim Schessl et al., *Infections and Vaccinations Preceding Childhood Guillain-Barre Syndrome: A Prospective Study,* 165 EUR. J. PEDIATR. 506 (2006) (Ex. 24)).)

Dr. Shafrir cites a number of case reports identifying post-tetanus vaccine GBS. (Ex. 15, pp. 33-33 (citing Kannikar Kongbunkiat et al., *Clinical Manifestations and Outcomes of Guillain-Barre Syndrome After Diphtheria and Tetanus Vaccine (dT) During a Diphtheria Outbreak in Thailand: A Case Series,* 19 NEUROL. ASIA 137 (2014) (Ex. 28); Rohit Bakshi & Michael Graves, *Guillain-Barre Syndrome After Combined Tetanus-Diphtheria Toxoid Vaccination,* 147 J. NEUROL. SCI. 201 (1997) (Ex. 29); Hussam Ammar, *Guillain-Barre Syndrome After Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine: A Case Report,* 5 J. MED. CASE REP. 1 (2011) (Ex. 30); Norris Newton Jr. & Abdorassol Janati, *Guillain-Barre Syndrome After Vaccination with Purified Tetanus Toxoid,* 80 SOUTH MED. J. 1053 (1987) (Ex. 31); W. Baust et al., *Peripheral Neuropathy After Administration of Tetanus Toxoid,* 222 J. NEUROL. 131 (1979) (Ex. 32); J.D. Pollar & G. Selby, *Relapsing Neuropathy Due to Tetanus Toxoid,* 37 J. NEUROL. SCI. 113 (1978) (Ex. 33)).) He also cites a study finding an increased risk of CIDP relapse following tetanus vaccination. (J. Pritchard et al., *The Risk of Relapse of Guillain-Barre Syndrome or Chronic Inflammatory Demyelinating Polyradiculo-Neuropathy Following Immunization,* 73 J. NEUROL. NEUROSURG. PSYCHIATRY 348 (2002) (Ex. 34).) That study screened 1,114 patients with either GBS or CIDP for reports of neurological symptoms post-vaccination. (*Id*. at 348.) Most of the patients, 927, suffered GBS, while an additional 179 suffered CIDP. Of those patients, 311 reported having received a vaccine subsequent to developing GBS and 65 reported having received a vaccine subsequent to developing CIDP. Of those vaccinated patients, 11 of the GBS patients and five of the CIDP patients reported a relapse in symptoms. (*Id*. at 349-50.) Overall, the authors concluded that the risk of relapse was "low" and stressed that many more patients received the same vaccines without relapse. (*Id*. at 350.) However, while cautioning that the sample size for CIDP cases

[19] The Canadian study by Top et al., examined 246 hospitalizations between 1996 and 2012, finding 24 cases where onset occurred within 30 days of an immunization. (Top et al., *supra,* at Ex. 23, p. 1411.) Among those cases, 19 cases had a single preceding vaccination, including diphtheria-tetanus-pertussis vaccine and influenza vaccine each in five cases respectively, various hepatitis B vaccines in four cases, meningococcal vaccine in three cases, and MMR vaccine in two cases. (*Id*. at 1412.) Among cases with co-administered vaccines, DPT was present in four cases and meningococcal was present in one. (*Id*.) Thus, Dr. Shafrir notes that tetanus-containing vaccine was the most frequently observed vaccine in the study. (Ex. 15, p. 32.) Importantly, however, the study authors note that a majority of these post-vaccination cases also had symptoms of recent infection, with 21% having microbiologically confirmed infection. (Top et al., *supra,* at Ex. 23, p. 1412.) The authors conclude the temporal association observed between vaccination and immunization is "most likely coincidental." (*Id*. at 1413.) The other study cited by Dr. Shafrir, Schessl et al., examined 84 cases of GBS among children and found that eight cases had preceding vaccinations; however, as with Top et al., they observed that a majority of those children, six of eight, had concomitant infections. (Schessl et al., *supra,* at Ex. 24, p. 605.)

was small, the authors indicated that among the CIDP patients "[o]f greatest concern is the risk of relapse following tetanus toxoid, which was 8.7% (95% CL 1.7%, 28.9%) in our patient sample. In view of these figures and previous reports of relapse of CIDP following tetanus toxoid patients may wish to avoid routine tetanus toxoid immunization." (*Id*.) Additionally, given that influenza vaccine is well accepted in this program as a cause of GBS, it is very interesting to note that among this population there were relatively higher rates of relapse following tetanus vaccine among both GBS and CIDP patients than there were following influenza vaccination.[20] (*Id*. at 349 (Table 1).) Given this, Dr. Shafrir cites several sources that suggest that tetanus toxoid is generally considered a risk factor for CIDP relapse. (Ex. 15, p. 34 (citing Robert Hadden & Richard Hughes, *Management of Inflammatory Neuropathies,* 74 J. NEUROL. NEUROSURG. PSYCHIATRY 1 (2003) (Ex. 35); Malcolm Rabie & Yoram Nevo, *Childhood Acute and Chronic Immune-Mediated Polyradiculoneuropathies,* 13(3) EUR. J. PAEDIATR. NEUROL. 209 (2009); Richard A.C. Hughes et al., *Immunisation and Risk of Relapse of Guillain-Barre Syndrome or Chronic Inflammatory Demyelinating Polyradiculoneuropathy,* 19 MUSCLE & NERVE 1230 (1996) (Ex. 37)).)

Further to this, Dr. Shafrir explains that tetanus disease is itself associated with peripheral neuropathies generally and GBS specifically has been documented as a complication. (Ex. 15, pp. 34-35 (citing Manik Shahani et al., *Neuropathy in Tetanus,* 43 J. NEUROL. SCI. 173 (1979) (Ex. 38); Jae Hoon Lee et al., *Generalized Tetanus Could Be Complicated with Guillain-Barre Syndrome,* 48 INTL. J. INFECT. DIS. 20 (2016) (Ex. 39)).) The IOM recognizes the effects of a natural infection as one type "albeit minor" of mechanistic evidence potentially supportive of vaccine causation, though "[e]vidence consisting only of parallels with the natural infections is never sufficient." (2012 IOM Report, *supra,* at Ex. E, p. 13.) Dr. Shafrir further stresses, for example, that the Vaccine Injury Table recognizes tetanus vaccines as a cause of brachial neuritis.[21] (*Id*. at 33.)

Finally, Dr. Shafrir relies on several regulatory warnings as evidence supporting a causal relationship between GBS and both the Tdap and meningococcal vaccines. The vaccine package inserts for both of the vaccines petitioner received, Adacel and

[20] Specifically, among GBS patients, 8 out of 2011 patients who received a flu vaccine and 6 out of 105 patients who received a tetanus vaccine reported a relapse. That works out to 3.8% and 5.7% of vaccinated patients respectively, a higher percentage for the tetanus vaccine. Likewise, among CIDP patients, 2 out of 46 patients who received a flu vaccine reported a relapse whereas the same number of patients who received a tetanus vaccine reported a relapse despite half as many patients (23) having received a tetanus vaccine. Thus, 4.3% of flu vaccine receipts and 8.7% of tetanus vaccine recipients suffered a relapse. (Pritchard et al., *supra,* at Ex. 34, p. 349 (Table 1).)

[21] In the 1994 IOM report filed by respondent, the IOM explained that two large case series had found a significant portion of subjects suffered brachial neuritis temporally related to a tetanus toxoid vaccine. (1994 IOM Report*, supra,* at Ex. G.) The IOM noted that the mechanism of brachial neuritis is not well understood, but that the case series were sufficient to extrapolate an excess risk for brachial neuritis following vaccine administration as compared to background rates. (*Id.*) Therefore, the committee concluded that "evidence favors acceptance of a causal relation between tetanus toxoid and brachial neuritis." (*Id*. at 112.)

Menactra, include a warning that persons previously diagnosed with GBS may be at increased risk of GBS following receipt of the vaccine.[22] (*Menactra, Meningococcal Polysaccharide Diphtheria Toxoid Conjugate Vaccine,* Package Insert, Sanofi Pasteur, pp. 44-5 (Ex. 44) (hereinafter "Menactra Package Insert"); *Adacel, Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine,* Package Insert, Sanofi Pasteur, p. 4 (Ex. 48) (hereinafter "Adacel Package Insert").) Additionally, the CDC advised in an October 20, 2006 MMWR that case reports exist to indicate "a possible association" between meningococcal vaccine and GBS.[23] (*Update: Guillain-Barre Syndrome Among Recipients of Menactra Meningococcal Conjugate Vaccine—United States, June 2005-Septemeber 2006,* 55 MMWR WKLY. 1120 (Ex. 17) (hereinafter "Menactra CDC Report").) Dr. Shafrir notes that Australia's regulatory agency has added GBS as a contraindication for administration of Menactra. (*Australian Public Assessment Report for Groups A, C, Y and W-135 Meningococcal Polysaccharide*

[22] The warning included in the Adacel package insert is based on the 1994 IOM report that found evidence to support a causal relationship between tetanus toxoid and GBS, as previously discussed in prior cases such as *Mohamad,* 2022 WL 711604. (Adacel Package Insert, *supra,* at Ex. 48, p. 4.) Adacel was initially approved in 2005, prior to the publication of the 2012 IOM report that revisited that conclusion. (*Id*. at 2.) Notably, however, the package insert filed in this case includes a notation regarding "recent major changes" that confirms the warnings and precautions section of the insert was updated in September of 2017. (*Id*.) The update that was made appears to relate to latex allergies. (*Id*. at 2, 4.) GBS was identified as an adverse reaction in post marketing experiencing but was not specifically addressed in the clinical trials. As of August 6, 2021, the most recent Vaccine Information Statement by the CDC continues to indicate, consistent with the warning contained in the Adacel prescribing information, that those considering at DTaP vaccine should talk with their healthcare provider before receiving the vaccine if they have ever had GBS. *DTaP (Diphtheria, Tetanus, Pertussis) Vaccine: What You Need to Know,* CDC, www.cdc.gov/vaccines/hcp/vis/vis-statements/dtap.pdf (last accessed on Feb, 17, 2023). The warning included in the Menactra insert is based on a prior MMWR from 2006, which petitioner has separately filed as Exhibit 17, and which is an update to the MMWR previously discussed in *Whitener,* 2009 WL 3007380, as well as a 2010 study by Harvard Medical School. The details of the Harvard study are not discussed in the insert and no author or publication are listed. Respondent has filed a 2012 paper by researchers affiliated with Harvard/Pilgrim that found no association between meningococcal vaccine and GBS. (Priscilla Velentgas et al., *Risk of Guillain-Barre Syndrome After Meningococcal Conjugate Vaccination,* 21 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 1350 (2012) (Ex. CC).) As with Adacel, GBS is included within the post marketing experience for Menactra; however, the risk of GBS was also evaluated in a retrospective cohort study that found no instances of Menactra having been administered within 42 days of symptom onset. (Menactra Package Insert, *supra,* at Ex. 44, p. 22.)

[23] This was based on VAERS case reports of GBS occurring within six weeks of vaccination. A prior MMWR had reported eight cases occurring between June and July of 2005. The October 2006 MMWR reported nine additional cases occurring between March and September of 2006. (Menatrca CDC Report, *supra,* at Ex. 17, p. 1.) The CDC compared 15 confirmed GBS cases in persons aged 11-19 and compared that against the 5.39 million vaccine doses administered and determined a rate of 0.20 cases of GBS per 100,000 person-months. To determine a background rate, the CDC used data from the Healthcare Cost and Utilization Project (HCUP), and estimated incidence of GBS of 0.11 per 100,000 person-months. Thus, the ratio of post-meningococcal vaccine GBS was 1.78 compared to the background rate with a 95% confidence interval of 1.02-2.85. (*Id*. at 3.) However, when the same calculation was done using information from the Vaccine Safety Database to determine the background rate, the result did not reach statistical significance. (*Id*. at 3-4.) The report notes that "substantial uncertainty exists regarding the risk estimate" and that a larger study would be necessary to reach a more definitive conclusion. (*Id*. at 4.)

Diphtheria Toxoid Conjugate Vaccine, TPA, pp. 87-88, https://www.tga.gov.au/sites/default/files/auspar-menactra-110929.pdf (Ex. 18).)

b. Petitioner's Immunologist, Omid Akbari, Ph.D.[24]

Petitioner filed two reports by immunologist Omid Akbari. (Exs. 65, 120.) Dr. Akrbari presents a theory of molecular mimicry, which he defines as "the mechanism by which an immune stimulated response by infection or other method, i.e., vaccination, can trigger cross-reactive T cells that cause the symptoms of autoimmune disease." (Ex. 65, p. 3.) Theories of molecular mimicry are most often supported by a demonstrated sequence homology and evidence of cross-reaction. (*Id.* at 3-8.) However, Dr. Akbari stresses that showing an identical or homologous sequence has a shared level of identity to a human protein implicated in a pathogenic process is only one possible method of implicating molecular mimicry as the mechanism involved in causing an autoimmune disease like GBS. (*Id.* at 9.)

Traditionally, immunologists have classified immune responses into two mechanisms: innate and adaptive. (Ex. 65, p. 5.) However, Dr. Akbari stresses that newly identified cells under the category of Innate Like Lymphocytes (ILL), consisting of several members including fast-acting NKT cells, Innate Like Lymphocytes (ILCs), and gamma delta T cells. (*Id.* (citing Luc Van Kaer et al., *Innate, Innate-Like and Adaptive Lymphocytes in the Pathogenesis of MS and EAE,* 16(6) CELL. MOL. IMMUNOL. 531 (2019) (Ex. 79); Lewis Lanier, *Shades of Grey—The Blurring View of Innate and Adaptive Immunity,* 13 NAT. REV. IMMUNOL. 73 (20130 (Ex. 80); Christopher Klose & David Artis, *Innate Lymphoid Cells Control Signaling Circuits to Regulate Tissue-Specific Immunity,* 30 CELL RES. 475 (2020) (Ex. 81)).) These cells, Dr. Akbari explains, are fast acting cells that can produce cytokines and cause protection or cause pathologies within hours. (Ex. 65, pp. 5-6.) Studies on other ILLs, including gamma-delta T cells and NKT cells, suggest that there are "no clear boundaries between innate and adaptive immunity." (*Id.* (citing Van Kaer et al., *supra,* at Ex. 79).) Dr. Akbari notes that ILLs have not previously been considered key participants in the early immune response; however, many recent observations suggest their involvement of these fast-acting immune cells in induction of demyelinating diseases, like GBS. (Ex. 65, p. 6.) For example, he suggests that activated gamma delta T cells in GBS patients may be

[24] Dr. Akbari received in his Master of Science in medical and general microbiology from the University College London. (Ex. 66, p. 1.) He received his Ph.D. in cellular and molecular immunology from the National Institute for Medical Research in London. (*Id.*) Dr. Akbari currently serves as a professor of medicine and professor of allergy and immunology at the Keck School of Medicine, University of Southern California. (Ex. 65, p. 2.) He also serves as an adjunct professor in the department of pediatrics at the David Geffen School of Medicine at UCLA and holds an active adjunct professorship in the department of immunology with Chiba University in Japan. (*Id.*) His research focuses on "the role of immune cells that induce autoimmune and allergic diseases." (*Id.*) Dr. Akbari's work has been published in the *New England Journal of Medicine*, *Nature Immunology*, *Nature Medicine, Nature Communications, Immunity and Journal of Clinical Investigation.* (*Id.*) He has received several national and international grants, including from the National Institute of Health. (*Id.*) Dr. Akbari serves as a reviewer for more than 25 research journals and has served on several NIH study sections involving Vaccines, Immunization, Allergy and Immunology research. (Ex. 65, p. 3.)

activated by the recognition of non-protein antigens in an MHC-unrestricted manner and contribute to the immune response to glycolipids that is a hallmark of GBS. (*Id.* (citing Giovanna Borsellino et al., *Phenotypic and Functional Properties of γδ T Cells from Patients with Guillain Barre Syndrome,* 102 J. NEUROIMMUNOL. 199 (2000) (Ex. 82)).) Borsellino et al. concluded that the Vδ1 subset of gamma delta T cells was the most prevalent in GBS, as it has been found to be at three times its normal numbers in patients. (Ex. 120, p. 3 (citing Borsellino et al., *supra,* at Ex. 82).)

Alternatively, Dr. Akbari proposes another member of these fast-acting ILLs—the innate ILCs. (Ex. 120, p. 3.) ILCs lack a recombined antigen receptor and are poised to produce interferon-gamma or T helper 2 (TH2) and TH17 cell-associated cytokines following stimulation. (*Id.*) Dr. Akbari relies on two studies. The first is a study showing that ILC2s are able to cause demyelination in a mouse model of MS. (*Id.* (citing Satoshi Hirose et al., *Type 2 Innate Lymphoid Cells Induce CNS Demyelination in an HSV-IL-2 Mouse Model of Multiple Sclerosis,* 23 ISCIENCE 1 (2020) (Ex. 127)).) Dr. Akbari stresses that ILCs have been shown to exert a profound influence in CNS inflammatory disease and as these cells are residents within the nervous system, they can be activated early in disease to express a wide variety of disease-modifying cytokines and chemokines. (Ex. 120, p. 3 (citing Melissa A. Brown & Rebecca B. Weinberg, *Mast Cells and Innate Lymphoid Cells: Underappreciated Players in CNS Autoimmune Demyelinating Disease,* 9 FRONT. IMMUNOL. 1 (2018) (Ex. 83)).) A second study cited by Dr. Akbari showed that a subset of fast acting-ILCs expressing T-bet greatly influenced the development of demyelinating and autoimmune disease. (Ex. 120, p. 3 (citing Brandon Kwong et al., *Author Correction: T-bet-dependent NKp46(+) Innate Lymphoid Cells Regulate the Onset of TH17-Induced Neuroinflammation,* 18 NAT. IMMUNOL. 1 (2018) (Ex. 84)).)

Dr. Akbari explains that current tetanus vaccines are made using the inactivated tetanus toxin, termed tetanus toxoid, and are extremely effective in generating serum anti-toxin antibodies which protect against the highly potent neurotoxin released upon infection by *Clostridium tetani.* (Ex. 65, p. 12.) Exposure of tetanus toxin to formalin or formaldehyde and Lysine solutions is the current method for preparation in vaccine manufacturing, which Dr. Akbari explains inactivates the toxin in a manner which leaves the native conformation of the protein stable. (*Id.*) He opines that tetanus toxin and tetanus toxoid are known to bind to cell surface gangliosides in the nervous system and mutational analysis of the toxin protein has shown that the binding properties of tetanus to gangliosides and to neuronal cells is due to the H_c chain (heavy chain) of the protein. (*Id.* (citing Rui Yu et al., *A Conformational Change of C Fragment of Tetanus Neurotoxin Reduces Its Ganglioside-Binding Activity but Does Not Destroy Its Immunogenicity,* 18 CLIN. VACCINE IMMUNOL. 1668 (2011) (Ex. 109); JJ Farrar et al., *Tetanus,* 69 J. NEUROL. NEUROSURG. PSYCHIATRY 292 (2000) (Ex. 110)).)

According to Dr. Akbari, several studies have shown that tetanus toxoid molecules are antigenically complex and capable of cross-reactivity with various biomolecules including DNA and bacterial toxins. (Ex. 65, p. 12 (citing Aleksandra Inic-Kanada et al., *Murine Monoclonal Antibody 26 Raised Against Tetanus Toxoid Cross-*

Reacts with Beta2-Glycoprotein I: Its Characteristics and Role in Molecular Mimicry, 61 AM. J. REPROD. IMMUNOL. 39 (2006) (Ex. 111); Behzod Dolimbek et al., *Cross Reaction of Tetanus and Botulinum Neurotoxins A and B and the Boosting Effect of Botulinum Neurotoxins A and B on a Primary Anti-Tetanus Antibody Response,* 31 IMMUNOL. INVEST. 247 (2002) (Ex. 112); P. Kursula, *Structural Properties of Proteins Specific to the Myelin Sheath,* 34 AMINO ACIDS 175 (2008) (Ex. 113)).) He cites one study where human volunteers were given booster immunizations to diphtheria and tetanus vaccines, and serum samples were collected one-week post immunization. (Ex. 65, pp. 12-13.) Analysis of human monoclonal antibodies derived from those blood samples showed that the antibodies collected from people one-week post-immunization were capable of cross-reacting to epitopes from self-antigens as well as to antigens derived from tetanus and diphtheria toxoid. (*Id.*) Dr. Akbari stresses that this study proves that antibodies derived from immunization with tetanus toxoid and diphtheria toxoids are capable of binding to self-antigens. (*Id.* (citing Dolimbek et al., *supra,* at Ex. 112; Kursula, *supra,* at Ex. 113).) Moreover, a study from Volk et al. determined that the tetanus toxoid consists of at least 20 different distinct sites (epitopes) that can be recognized by the immune system. (Ex. 65, p. 13 (citing W.A. Volk et al., *Neutralization of Tetanus Toxin by Distinct Monoclonal Antibodies Binding to Multiple Epitopes on the Toxin Molecule,* 45 INFECT. IMMUN. 604 (1984) (Ex. 114)).)

Dr. Akbari's opinion focuses on the ability of the tetanus toxoid to cross-react with known pathogenic molecules already identified in GBS patients. He does not address the research showing that the diphtheria or pertussis components of the vaccine could also result in an adverse cross-reaction; however, he opines that this is also plausible. (Ex. 65, p. 13.) He cites a study using BLAST which revealed that myelin P0 has sequence and structural similarity to the diphtheria toxin, among other putative pathogens. (*Id.* (citing Deena Vardhini et al., *Comparative Proteomics of the Mycobacterium Leprae Binding Protein Myelin P0: Its Implication in Leprosy and Other Neurodegenerative Diseases,* 4 INFECT. GENET. EVOL. 21 (2004) (Ex. 115)).) According to Dr. Akbari, this research implicates other components of the vaccines as well in the pathogenesis of GBS. (Ex. 65, p. 13.)

In response to Dr. Platt, Dr. Akbari opines that the literature describing the quick onset of ILLs or memory cells supports the 24-hour onset in petitioner's case. (Ex. 120, p. 5.) For instance, Dr. Akbari notes that a recent study showed that inflammatory neuropathies display disease and subtype-specific alterations of CSF cell composition and increased number of memory lymphocytes and ILLs (including NKT cells) play a major role in the acute onset of GBS. (*Id.* (citing Michael Heming et al., *Immune Cell Profiling of the Cerebrospinal Fluid Provides Pathogenetic Insights into Inflammatory Neuropathies,* 10 FRONT. IMMUNOL. 1 (2019) (Ex. 85)).) Other GBS literature supports a quick onset as well. (Laura Polakowski et al., *Chart Confirmed Guillain-Barre Syndrome After 2009 H1N1 Influenza Vaccination Among the Medicare Population, 2009-2010,* 178 AM. J. EPIDEMIOL. 962 (2013) (Ex. 129); Silvia Perez-Vilar et al., *Guillain-Barre Syndrome After High-Dose Influenza Vaccine Administration in the United States, 2018-2019 Season,* 223 J. INFECT. DIS. 416 (2021) (Ex. 130)).) Perez-Vilar et al. found that 97.9% of cases developed GBS symptoms within 3 weeks post-vaccination and more

than half of cases (54.2%) occurred within 0-2 days after vaccination. (Ex. 120, p. 5 (citing Perez-Vilar et al., *supra,* at Ex. 130, Figure 2C).)

c. Respondent's Neurologist, Leslie Benson, M.D.[25]

Respondent filed one expert report from Dr. Benson. (Ex. A.) Dr. Benson opines that all of petitioner's symptoms, including ptosis, extremity paresthesia, weakness and progressive areflexia are consistent with his diagnosis of GBS. (Ex. A, p. 4.) However, Dr. Benson stresses that the timing of onset is not medically appropriate for vaccine-causation where petitioner's GBS onset occurred less than 24 hours after his subject vaccinations. Instead, Dr. Benson opines that petitioner's neurological symptoms began with pain in his hands on July 9th around 12:00 PM and progressed to unilateral ptosis later in the same day. (*Id.* at 1 (citing Ex. 4, p. 43, 50, 56, 64, 73.) Dr. Benson stresses that pain and paresthesia are common in childhood GBS. (Ex. A, p. 5.) She stresses that paresthesia is a common initial (34%) and later (79%) manifestation of pediatric GBS. (*Id.* (citing Monique Ryan, *Epidemiology, Clinical Features, and Diagnosis of Guillain-Barre Syndrome in Children,* UPTODATE 1 (2019) (Ex. T); Hugh Willison et al., *Guillain-Barre Syndrome,* 388 LANCET 717 (2016) (Ex. V)).) Thus, petitioner's neuropathic pain and paresthesia are the initial manifestations of petitioner's GBS.

Dr. Benson opines that petitioner's ptosis is a manifestation of his GBS and Miller Fisher syndrome and is not a separate vaccine reaction. (Ex. A, p. 5.) Dr. Benson explains that ptosis is a form of ophthalmoparesis that can be associated with forms of GBS. (*Id.* (citing Mazen Dimachkie & Richard Barohn, *Guillain-Barre Syndrome and Variants,* 31 NEUROL. CLIN. 491 (2013) (Ex. K); Ryan, *supra,* at Ex. T).) In petitioner's case his ptosis *did* evolve into frank ophthalmoparesis, as documented by his ophthalmologist, which all fits with the evolution of ocular manifestations of GBS. (Ex. A, p. 5 (citing Ex. 4, p. 73).)

Dr. Benson contends that current scientific evidence supports no relationship between Menactra or Tdap vaccinations and GBS. (Ex. A, p. 5.) While there is some link between the older 1976 influenza vaccine and post-vaccination GBS, Dr. Benson stresses that the link between infection and GBS is clearly much stronger. (*Id.* (citing Lamiae Grimaldi-Bensouda et al., *Guillain-Barre Syndrome, Influenzalike Illnesses, and Influenza Vaccination During Seasons with and Without Circulating A/H1N1 Viruses,* 174 AM. J. EPIDEMIOL. 1 (2011) (Ex. Z); Nicola Principi & Susanna Esposito, *Vaccine-Preventable Diseases, Vaccines, and Guillain-Barre Syndrome,* 37 VACCINE 5544

[25] Dr. Benson received her Bachelor of Science degree from Colorado State University and her M.D. from the University of Colorado Health Sciences Center. (Ex. B.) She is a pediatric neurology board certified physician with subspecialty fellowship training in neuro-immunology, licensed to practice medicine in the state of Massachusetts. (Ex. A, p. 1.) She is the assistant director of the multiple sclerosis and related disorders and neuro-immunology clinics at Boston Children's Hospital. (*Id.*) She has authored / coauthored thirty-seven peer reviewed articles and three chapters and three review articles regarding pediatric neuroinflammatory disease. (*Id.*) She treats children with neuroinflammatory diseases in both the inpatient and outpatient settings. (*Id.*)

(2019) (Ex. AA)).) She stresses that MCV, tetanus, diphtheria and pertussis have been "only coincidentally linked to GBS with no causal association based on the latest literature." (Ex. A, p. 5.) Dr. Benson suggests that "[a]lthough long term, large scale data looking for vaccine associated complications for both vaccines that [petitioner] received exists, Dr. Shafrir presents predominantly small scale, basic science, old data and case reports to support his arguments." (*Id.*) Dr. Benson also discounts the value of the VAERS report filed in petitioner's case because petitioner's "ID physician notified multiple state health departments due to public health concern, similar to [a] report to VAERs." (*Id.*) She stresses that it is a physician's duty to consider alternative diagnoses and triggers, and in both instances petitioner's physicians were "covering their bases while evaluating the possibilities." (*Id.* (citing Ex. 4, pp. 140-141).)

For the Menactra vaccine specifically, Dr. Benson stresses that the initial reports of post-vaccination GBS occurred within 1.5 to 5 weeks of vaccination after the vaccine was approved in 2005. (Ex. A, p. 5.) This led to warnings via MMWR reports. (*Id.*) However, she stresses that large scale follow-up studies have not found a true association between GBS and meningococcal vaccination. (*Id.*) In fact, Dr. Benson emphasizes the warning was removed in 2011. (*Id.* (citing Michael Apicella, *Meningococcal Vaccines,* UPTODATE 1 (2018) (Ex. BB); Priscilla Velentgas et al., *Risk of Guillain-Barre Syndrome After Meningococcal Conjugate Vaccination,* 21 PHARMACOEPIDEMIOL. & DRUG SAF. 1350 (2012) (Ex. CC); Tanya Myers & Michael McNeil, *Current Safety Issues with Quadrivalent Meningococcal Conjugate Vaccines,* 14 HUM. VACCIN. & IMMUNOTHER. 1175 (2018) (Ex. DD)).)

For the Tdap vaccine, Dr. Benson notes that the 1978 Pollard case of recurrent neuropathy following booster immunization received attention for a possible vaccine-specific GBS trigger. (Ex. A, p. 6.) However, a follow-up study in 1997 examined the predicted baseline incidence of GBS among children (2.4 cases) compared to the actual incidence found within a DTP vaccination cohort (2 cases within 6 weeks of vaccination). (*Id.* (citing Jessica Tuttle et al., *The Risk of Guillain-Barre Syndrome After Tetanus-Toxoid-Containing Vaccines in Adults and Children in the United States,* 87 AM. J. PUBLIC HEALTH 2045 (1997) (Ex. KK)).) Dr. Benson suggests that the rate of GBS in that study among those receiving vaccination "was actually lower than expected in both adults and children cohorts." (*Id.*) Moreover, the Pollard case was reclassified from GBS to CIDP by the IOM in 2012. (Ex. A, p. 6 (citing IOM Report 2012, *supra,* at Ex. E).)

Dr. Benson further stresses that the time between vaccinations to symptom onset was less than 24 hours. (Ex. A, p. 6.) She insists that "[l]ess than 24 hours is not long enough for manifestation of a systemic auto-immune response, particularly one of molecular mimicry and antibody production." (*Id.*) The Adams and Victor textbook observes that "infection or immunization precedes the neuropathic symptoms by 1 to 3 weeks in approximately 60 percent of cases . . . almost every known febrile infection and immunization has at one time or another been reported to precede GBS (some probably coincidentally)." (*Id.* (quoting Ropper et al., *supra,* at Ex. 21).) While another source cites a median interval from vaccination to symptom onset of 18 days, with a

range of 4-30 days. (Ex. A, p. 6 (citing Top et al., *supra,* at Ex. 23).) Dr. Benson concludes that the references provided from Dr. Shafrir are outdated single case reports "which do not offer good assessment of causality" or focus on an alternative disease CIDP. (Ex. A, pp. 6-7.)

Lastly, Dr. Benson suggests that the lack of infectious work-up precludes eliminating infection as an inciting trigger in petitioner's case. (Ex. A, p. 7.) Dr. Benson acknowledges that there is no documentation of prior infectious symptoms prior to petitioner's GBS onset, but she stresses that tests were not done to rule out *c. jejuni* or EBV. (*Id.*) She observes that EBV can be asymptomatic and cause transaminitis. (*Id.*) In petitioner's case, Dr. Benson opines that his transaminitis may have been related to illness / medications in the ICU, however an infectious etiology for petitioner's GBS cannot be ruled out. (*Id.*) According to Dr. Benson, the significance of the positive throat culture for strep "is uncertain in this case." (*Id.*) She suggests that "[t]here have been a few reported cases of Miller Fisher syndrome associated with strep" though it is not a common pathogen listed in association with GBS. (Ex. A, p. 7.) "That said, like those 2 cases, that infection triggered [petitioner's] GBS." (*Id.*) She notes that Dr. Brown likewise posited this theory. (*Id.* (citing Ex. 4, p. 619).)

d. Respondent's Immunologist, Craig D. Platt, M.D., Ph.D.[26]

Respondent filed three expert reports from Dr. Platt. (Exs. C, RR, UU.) Dr. Platt's first report responds to Dr. Shafrir's expert report and offers many of the same points made in Dr. Benson's expert report. (*See* Exs. A, C.) Dr. Platt stresses three points: (i) a link between vaccination and GBS has not been established (ii) the timing of symptom onset is not biologically plausible and (iii) a more plausible trigger for GBS in this case was petitioner's streptococcal infection. (Ex. C, p. 4.) To the first point, Dr. Platt highlights the conclusions from Haber et al. (2009), an oft-cited study in this Program. (*Id.* at 5.) Haber et al. concluded that the evidence for causal association to GBS is strongest for the swine influenza vaccine that was used in 1976-77, though studies of influenza vaccines used in subsequent years, "have found small or no increased risk of GBS." (*Id.* (quoting Penina Haber et al., *Vaccines and Guillain-Barre Syndrome,* 32 DRUG SAFETY 309 (2009) (Ex. F)).) Haber et al. also found no correlation between oral polio vaccine or tetanus -toxoid-containing vaccines and GBS (despite the earlier IOM report). (*Id.; see also* 2012 IOM Report, *supra,* at Ex. E.) To the second point, Dr. Platt stresses that in the only case report cited by Dr. Shafrir where neurological symptoms started the day after vaccination, the authors themselves did not find it likely that GBS was vaccine-caused. (Ex. C, p. 7 (citing Schessl et al., *supra,* at Ex. 24).) In that patient with a one-day onset, the authors note that the onset was "too

[26] Dr. Platt is a clinical immunologist with board certification in Allergy and Clinical Immunology working at Boston Children's Hospital. (Ex. D.) He earned his M.D. and Ph.D. in Immunobiology from the Yale School of Medicine. (*Id.*) His clinical expertise is in the diagnosis and treatment of allergic and immunologic diseases. (Ex. C, p. 1.) In his practice, he evaluates and treats patients with a broad range of immune-mediated diseases including autoimmune, hypersensitivity and immunodeficiency disorders. (*Id.*) He frequently treats patients with various reactions to drugs and vaccines. (*Id.*) His Ph.D. research was on the cellular biology of dendritic cells, which are required for the initiation of adaptive immune responses. He has co-authored over twenty peer reviewed articles and three book chapters. (*Id.*)

short to warrant a causal relationship."[27] (Schessl et al., *supra,* at Ex. 24, p. 610.) Finally, Dr. Platt opines that petitioner's streptococcal infection was a more plausible trigger for GBS. (Ex. C, pp. 8-10 (citing Nobuhiro Yuki & Koichi Hirata, *Fisher's Syndrome and Group A Streptococcal Infection,* 160 J. NEURO. SCI. 64 (1998) (Ex. M)).) While not a common trigger for GBS, Dr. Platt indicates that infection has at least two features that vaccines do not, making it a more likely trigger: (1) a precedent for causing immune mediated disorders such as acute rheumatic fever and acute glomerulonephritis and (2) the features of pathogen replication, epitope spreading and antigen persistence that vaccines lack. (Ex. C, p. 10.)

In his second report, Dr. Platt agrees that protein sequence homology is not the only theory of molecular mimicry capable of demonstrating cross-reactivity. (Ex. RR, p. 3.) However, Dr. Platt disagrees that direct evidence supports a causal link between GBS and tetanus toxoid. (*Id.* at 4.) He stresses that the Inic-Kanada et al. study found that certain subpopulations of antibodies raised against tetanus toxoid in mice are cross-reactive with b_2GPI. (*Id.* at 5 (citing Inic-Kanada et al., *supra,* at Ex. 111).) Dr. Platt responds, "[t]he development of such autoantibodies could theoretically induce a disorder call antiphospholipid syndrome, a clotting disorder, which is not relevant in this case." (Ex. RR, p. 6.) Next, Dr. Platt explains that Dolimbek et al. studied sera from nine individuals who had been vaccinated with tetanus vaccines for antibodies that bound to botulism toxoid as well. (*Id.* (citing Dolimbek et al., *supra,* at Ex. 112).) These results, according to Dr. Platt, show that antibodies against tetanus toxoid antibodies cross-react with botulinum neurotoxins—which does not demonstrate an association between tetanus toxoid immunization and risk of autoimmunity. (*Id.*) Kursula does not mention tetanus toxoid or vaccination in the article—instead the article focuses on structural properties of proteins within the myelin sheath. (*Id.* (citing Kursula, *supra,* at Ex. 113).)

Dr. Platt contends that there are no references showing that ILLs are tied to GBS pathogenesis. (Ex. RR, p. 4.) He acknowledges that the timeline between vaccination and disease onset is "theoretically possible by invoking innate immune cells, [but] there is no evidence provided that these cells are actually involved in GBS pathogenesis, so this remains an entirely theoretical model." (*Id.* at 10.) Dr. Platt disagrees that the Van Kaer article supports Dr. Akbari's theory. Dr. Platt stresses that Van Kaer comments on the role of ILLs in the pathogenesis of multiple sclerosis and experimental autoimmune encephalitis, but "this does not address how GBS would emerge on such a rapid timeframe." (*Id.*) He opines that there is no evidence for a model where ILLs could speed up the development of an adaptive immune response, or that molecular mimicry can occur more quickly due to the presence of innate like lymphocytes. (*Id.*)

In his final expert report, Dr. Platt accepts the premise that gamma delta T cells may play a role in the molecular mimicry response that has been established between *C. jejuni* and GBS. (Ex. UU, p. 4.) However, he opines that "it is not reasonable to infer from this that [gamma delta] T cells must therefore be driving GBS in response to

[27] That particular patient also suffered a concomitant upper respiratory infection. (Schessl et al., *supra,* at Ex. 24.)

tetanus vaccination." (*Id.*) Dr. Platt suggests that the reason Dr. Akbari invokes gamma delta T cells is to explain how a reaction to the tetanus vaccine could happen within one day of vaccination. (*Id.*) Yet, Dr. Platt recalls that *C. jejuni* infection typically occurs 1-4 weeks prior to GBS symptom onset. (*Id.*) In response to the theory involving ILCs, Dr. Platt likewise stresses that there is no reference to vaccination in any of the literature cited by Dr. Akbari. (Ex. UU, p. 4.) By focusing on the link between *C. jejuni* and GBS rather than on the proposed link between tetanus toxoid and GBS, Dr. Platt argues that petitioner's expert misses the mark. (*Id.*)

In regard to onset, Dr. Platt emphasizes that all of the studies cited by Dr. Akbari reference the influenza vaccine – not Tdap or Menactra. (Ex. UU, p. 5.) He also highlights the fact that the influenza vaccine is typically administered during fall and winter months when there is increased incidence of respiratory illnesses (that are associated with GBS). (*Id.*) Dr. Platt maintains that a number of well-performed studies suggest there is no link between GBS and influenza vaccine. (*Id.*)

VII. Analysis

a. *Althen* Prong One

Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received can cause the type of injury alleged. *Pafford*, 451 F.3d at 1355–56 (citations omitted). To satisfy this prong, petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id.* at 549. Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325-26 (Fed. Cir. 2006)). Scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Nonetheless, although petitioners cannot be *required* to show "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect" (*Capizzano*, 440 F.3d at 1325), the special master may consider and evaluate such evidence when filed. *Andreu,* 569 F.3d at 1379 (Special masters may consider medical literature and epidemiological evidence, when it is submitted, in "reaching an informed judgment as to whether a particular vaccine likely caused a particular injury.").

Based on this standard, and upon review of the record as a whole, I conclude that petitioner has met his preponderant burden of proof with respect to *Althen* prong one for the reasons discussed below. Specifically, I find that there is adequate evidence of record to demonstrate that Tdap vaccines can cause GBS. Petitioner's

experts offer further information regarding the ability of the Menactra vaccine to also cause GBS. However, it is unnecessary to reach those points to resolve this case.

i. Vaccine-Caused GBS Is Biologically Plausible

Context is important in evaluating petitioner's medical theory of causation in this case. Before reaching the particulars of petitioner's vaccine-specific theory, the following points are all evidenced on this record and are beyond meaningful dispute: GBS is an autoimmune condition. (Baxter et al., *supra,* at Ex. II, p. 1.) As an autoimmune condition, GBS is generally accepted to have multiple infectious triggers. (*Id.;* Ropper et al., *supra,* at Ex. 21.) Yet, among those triggers, only *c. jejuni* is accepted as having a demonstrated molecular mimic. (Haber et al., *supra,* at Ex. F, p. 311.) Further to these points, GBS has also been epidemiologically associated with at least two formulations of the influenza vaccine, a swine flu formulation from the 1970s and an H1N1 formulation from 2009, and has also been linked to an older version of a rabies vaccine. (1994 IOM Report, *supra,* at Ex. G; Haber et al., *supra,* at Ex. F.)

Because petitioners in this program are allowed to prove their cases circumstantially, and because experts in this program are permitted to engage in at least some extrapolation, the fact that GBS is well accepted as an autoimmune condition with a wide variety of suspected antigenic triggers, inclusive of antigens from both infection and vaccination, provides meaningful evidence supporting petitioner's burden of proof with respect to *Althen* prong one. That is, even before addressing any vaccine-specific evidence, this general understanding of GBS pathophysiology constitutes a reasonably strong starting premise for a claim that vaccines beyond the flu vaccine can be implicated as triggers of GBS.

Respondent's experts do not acknowledge the strength in this starting premise. In particular, both of respondent's experts contend that the evidence supporting petitioner's case cannot overcome the lack of epidemiologic support.[28] This suggests that they are requiring a degree of scientific confirmation that exceeds what petitioner is obligated to prove in this program and reduces the persuasive value of their competing opinions. Petitioners are not obligated to prove their case epidemiologically. Moreover, the IOM, which Dr. Platt in particular relies upon as persuasive, has consistently explained that epidemiology alone is not dispositive.

[28] Dr. Benson writes that "[a]lthough long term, large scale data looking for vaccine associated complications for both vaccines that [petitioner] received, Dr. Shafrir presents predominantly small scale, basic science, old data and case reports to support his arguments." (Ex. A, p. 5.) Dr. Benson charges that Dr. Shafrir is engaged in speculation because "[a]lthough much basic science literature is cited . . . no large scale human data is presented." (*Id*. at 6.) Dr. Platt similarly contends that "[i]t is essential to remember that given the millions of vaccinations administered each year, a number of patients who develop GBS will have received vaccination in the preceding weeks by chance alone. Therefore, to establish causality, case reports alone are not sufficient. Fortunately, careful analysis of the literature has been performed giving epidemiological weight only to studies that make use of control groups." (Ex. C, p. 5.) Dr. Platt contends that not even the link between the flu vaccine and GBS can be said to be "well established" and therefore "there is in fact no consensus that vaccines induce GBS." (*Id.* at 6-7.)

In assessing potential adverse events of vaccines, the IOM has consistently used a methodology that accepts a general background of biologic plausibility coupled with more specific, but generally more limited, evidence relating to the specific combination of vaccine and injury. This evidence may include epidemiology, but is not limited to epidemiology. Two comprehensive IOM reports are in evidence in this case. The 1994 IOM report and the 2012 report. (1994 IOM Report, *supra,* at Ex. G; 2012 IOM Report, *supra,* at Ex. E.) The 1994 report defines "evidence favor[ing] acceptance of a causal relationship" as follows:

> The balance of evidence from one or more case reports or epidemiologic studies provides evidence for a causal relation that outweighs the evidence against such a relation. Demonstrated biologic plausibility was considered supportive of a decision to accept a causal relation but insufficient on its own to shift the balance of evidence from other sources.

(1994 IOM Report, *supra,* at Ex. G, p. 33 (emphasis added).) Similarly, the 2012 IOM report reserved the category of "favors acceptance of a causal relationship" for those cases that had "either epidemiologic evidence of moderate certainty of an increased risk or by mechanistic evidence of intermediate weight." (2012 IOM Report, *supra,* at Ex. E, p. 18.) Mechanistic evidence of "intermediate weight" includes "[a]t least two cases, taken together, for which the committee concludes the vaccine *may be* a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with the relevant biological response to vaccine." (*Id*. at 14 (emphasis original).)[29]

Thus, while petitioner's burden of proof is not limited to demonstrating biologic plausibility,[30] the general background regarding the nature and causes of GBS is highly relevant. Dr. Shafrir and Dr. Akbari both invoke this background as partial support for their vaccine-specific causal opinions and, contrary to respondent's experts' view, that reliance is sound and reliable. Dr. Akbari's first report in particular provides extensive

[29] Applying these standards to the available evidence, the two IOM reports reached different conclusions with the respect to whether tetanus-containing vaccines can cause GBS. (Compare 1994 IOM Report, *supra,* at Ex. G; *and* 2012 IOM Report, *supra,* at Ex. E.) This difference is discussed separately below.

[30] The Federal Circuit has "consistently rejected theories that the vaccine only 'likely caused' the injury and reiterated that a 'plausible' or 'possible' causal theory does not satisfy the standard." *Boatmon*, 941 F.3d at 1360. This is not to be confused with what is "biologically plausible," which simply expresses that the point being made is consistent with existing medical knowledge. *E.g.*, *Doe93 v. Sec'y of Health & Human Servs.*, 98 Fed Cl. 553, 567 (2011) (collecting citations to cases where petitioners have been required to present a "biologically plausible" theory as that term is understood in the scientific community).); *accord Kottenstette v. Sec'y of Health & Human Servs*., 861 Fed. App'x 433, 440-41 (Fed. Cir. 2021) (assigning error where the Court of Federal Claims interpreted the special master's reference to "biologic credibility" as equivalent to the type of merely "plausible" theory presented in *Boatmon*.) A proposed theory must necessarily be biologically plausible (*i.e*., consistent with existing medical knowledge) in order to be "sound and reliable;" however, biologic plausibility is not itself the legal standard. *Boatmon,* 941 F.3d at 1359-60.

discussion of the immunology underlying GBS and autoimmunity more broadly that provides a theoretical framework for petitioner's *Althen* prong one showing.

ii. The 1994 IOM Report Provides Some Evidence to Support Petitioner's Claim and Is Not Automatically Outweighed by the 2012 Report

Further to this general biologic plausibility, Dr. Shafrir stressed, among many other points raised, that the prescribing information for Adacel Tdap vaccine at issue in this case includes a warning of the potential risk of post-vaccination GBS among those who previously suffered GBS. (Ex. 15, p. 32; Ex. 48, p. 4.) While these warnings are not admissions and do not in themselves constitute proof of causation, it does raise the question of whether it reflects a reasonable, ongoing concern.[31] The Adacel warning is based on the above-referenced 1994 IOM report. (Ex. 48, pp. 4, 27.) The 1994 IOM report concluded that "[t]he evidence favors a causal relation between tetanus toxoid and GBS. If the evidence favors a casual relation between tetanus toxoid and GBS, then in the committee's judgment the evidence favors a casual relation between vaccines containing tetanus toxoid (DT and Td) and GBS." (1994 IOM Report, *supra,* at Ex. G, p. 89.)

Ordinarily, recognition of a causal relationship by the IOM would be strong evidence favoring petitioner's claim. However, respondent argues that this report is, in effect, outdated. (ECF No. 76, p. 13.) In fact, respondent contends that to cite to an older IOM report is "misleading," because the prior IOM report has been "discredited" and the IOM has issued a more recent report that represents the IOM's current position.[32] (*Id*.) Petitioner disagrees. (ECF No. 77, pp. 7-8.)

Respondent's argument is reasonable in at least the general sense that the Vaccine Act envisions both that the Secretary will update the Vaccine Injury Table over time and that the Secretary will rely on the IOM to study the risks of vaccines covered by the program. § 300aa-2; § 300aa-5; § 300aa-14(c). In the ordinary course it can

[31] In some prior cases, special masters have concluded broadly that "[s]tatements contained in vaccine package inserts do not constitute reliable proof of causation, and cannot be deemed admissions that the vaccines in question have the capacity to harm a particular petitioner in a specific manner." *Sullivan v. Sec'y of Health & Human Servs.,* No. 10-398V, 2015 WL 1404957, at *20 (Fed. Cl. Spec. Mstr. Feb. 13, 2015) (citing *Werderitsh v. Sec'y of Health & Human Servs.,* No. 99-319V, 2005 WL 3320041, at *8 (Fed. Cl. Spec. Mstr. Nov. 10, 2005); *see also* 21 C.F.R. § 600.80(l). It has also been observed, however, that the fact that package inserts are not admissions does not prevent them from including information that does have value, in particular information provided by the clinical trials described by the package insert. *Cottingham v. Sec'y of Health & Human Servs.*, 15-1291V, 2021 WL 347020, *23-26 (Fed. Cl. Spec. Mstr. Jan. 7, 2021), *vacated on other grounds*, 154 Fed. Cl. 790 (2021).

[32] It should be noted that, although the Vaccine Act contemplates that the IOM's review will be highly relevant to the Secretary, the IOM's conclusion is not coextensive with the position of the government. For example, as discussed above, the special master in *Mohamad* discussed several other sources of governmental statement under the authority of the Secretary of Health & Human Services that are not consistent with the IOM's 2012 conclusion. 2022 WL 711604. With regard to whether the package warning is in itself outdated, see n. 22, *supra*.

generally be expected that a more up to date IOM review is likely to carry greater weight in that it should better reflect current scientific understanding. Thus, prior decisions by special masters have accepted the IOM's 2012 conclusion on the same question at issue here despite the existence of the prior report. *Howard v. Sec'y of Health & Human Servs.,* No. 16-1592V, 2022 WL 4869354, at *9 (Fed. Cl. Spec. Mstr. Aug. 31, 2022); *Sanchez v. Sec'y of Health & Human Servs.,* No. 18-1012V, 2022 WL 1013264, at *22 (Fed. Cl. Spec. Mstr. Mar. 11, 2022); *Rupert v. Sec'y of Health & Human Servs.*, No. 10-160V, 2014 WL 785256, at *7 (Fed. Cl. Spec. Mstr. Feb. 3, 2014). However, nothing in the Vaccine Act suggests that the 2012 report *automatically* controls. The 1994 and 2012 reports represent two independent reviews by two different committees and the 2012 report does not contain any explicit critique of the prior committee's work.[33] Both reports are in evidence in this case and the Vaccine Act does not dictate that a special master is bound by the conclusions of any particular IOM report. Indeed, as discussed above (*see* Section II), special masters may view the IOM as applying a standard for causation that exceeds what petitioners are obligated to prove and therefore do not treat the IOM's conclusions as dispositive. Thus, the substance of both reports should be weighed to assess their persuasive value rather than reflexively accepting the latest report to the exclusion of the earlier report. *Accord Mohamad*, 2022 WL 711604, at *9-18 (considering the 1994 IOM report among many other pieces of evidence and explaining that "the IOM's 2012 report did change its previous assessment, but not as drastically as sometimes suggested" and that "[w]hile [respondent's expert] is correct that the 2012 IOM report did not accept the theory that a tetanus vaccine can cause GBS, the IOM report also did not reject the proposition entirely").

In assessing the relationship between vaccination and GBS, the 1994 report included a lengthy discussion of the pathophysiology of demyelinating disorders broadly, and GBS specifically, accompanied by discussion of evidence linking GBS to both the swine flu vaccine and rabies vaccine. (1994 IOM Report, *supra,* at Ex. G, pp. 39-47.) The IOM concluded that "it is biologically plausible that injection of an inactivated virus, bacterium, or live attenuated virus might induce in the susceptible host an autoimmune response by deregulation of the immune response, by non-specific activation of the T cells directed against myelin proteins, or by autoimmunity triggered by sequence similarities of proteins in the vaccine to host proteins such as those of myelin." (*Id*. at 48, 87.) Although the 2012 report stops short of issuing any similar statement, it does not include any discussion that would refute the 1994 report's foundational understanding. (2012 IOM Report, *supra,* at Ex. E, pp. 71-73.) Much of the 2012 report's discussion of causal mechanisms confirms the same general

[33] A review of the committee assignments confirms that not a single member of the 1994 committee participated in the 2012 review. (*Compare* 1994 IOM Report, *supra,* at Ex. G, pp. 5-6, *and,* 2012 IOM Report, *supra,* at Ex. E, pp. 7-8.) The 1994 report is the result of the initial mandate included in the Vaccine Act that the IOM conduct a broad review of possible adverse events associated with vaccines commonly given in childhood. The 2012 study was the 12th time the IOM had conducted some review for this program, though it was the first comprehensive review since the original 1994 report. (2012 IOM Report, *supra,* at Ex. E, p. 11.) However, the 2012 report does not identify any specific prompt that caused the Secretary to request the convening of the 2012 committee. (2012 IOM Report, *supra,* at Ex. E, p. 32.)

principles of immunology. Similarly, but without extending to vaccination, the 2012 report stated in its weighing of mechanistic evidence that "[a]utoantibodies, complement activation, immune complexes, T cells, and molecular mimicry may contribute to the symptoms of GBS." (2012 IOM Report, *supra,* at Ex. E, p. 558.)

The 2012 report likewise did not identify any new evidence that refutes the older report or renders it out of date regarding the specific conclusion that tetanus-containing vaccines likely can cause GBS. The 2012 report identified four epidemiologic studies for its review of the topic that post-dated the 1994 report; however, the report concluded that *all four* studies had flaws that prevented them from contributing to the weight of epidemiologic evidence. (2012 IOM Report, *supra,* at Ex. E, p. 557.) Thus, the committee assessed the epidemiologic evidence as "insufficient or absent" to assess a causal link between GBS and Tdap vaccines. Therefore, it is not the case that any new epidemiology cast any doubt on the conclusion of the 1994 committee. The 2012 report also identified five publications of case reports post-dating the 1994 report. (2012 IOM Report, *supra,* at Ex. E, p. 557.) However, because case reports are by their very nature anecdotal, the existence of later, unpersuasive case reports does not call into question the conclusion of the 1994 report.

Thus, Dr. Platt's specific assertion that the 1994 report was "discredited" by later studies is unpersuasive. For this point, Dr. Platt cites to Haber et al., a 2009 paper that reviewed data related to GBS through 2008. (Ex. C, p. 6 (discussing Ex. F).) Dr. Platt quotes Haber as stating that the 1994 IOM conclusion that the evidence favors a relationship between GBS and tetanus-containing vaccines has been disproven by large scale epidemiologic studies that found no correlation. (*Id.*) He then goes on to buttress this point by noting that the IOM's 2012 report changed the IOM's position on the subject. (*Id*.) Unacknowledged by Dr. Platt, however, is that subsequent to the 2009 Haber review, the IOM in that very 2012 report concluded that there is insufficient epidemiology to assess the causal relationship at issue. (2012 IOM Report, *supra,* at Ex. E, p. 557.) Dr. Benson similarly relies on epidemiology that the IOM specifically rejected. (*Compare* Ex. A, p. 7 (citing Tuttle et al. (Ex. KK) in support of the assertion that the lack of an epidemiologic association is "clear")) *with* 2012 IOM Report, *supra*, at Ex. E, p. 557 (concluding that Tuttle et al., does not contribute to the weight of epidemiologic evidence).) Moreover, the 1994 IOM report's conclusion was not primarily an epidemiologic observation, and both the 1994 and 2012 IOM reports allow for mechanistic evidence to outweigh epidemiologic evidence.

Further to its foundational understanding of vaccine-caused demyelination, the 1994 report examined 29 prior cases of post-tetanus vaccine GBS, but found only three that were described in enough detail to be accepted as true post-vaccination cases of GBS. (1994 IOM Report, *supra,* at Ex. G, p. 87.) These were Hopf, 1980; Newton and Janati, 1987; and Pollard and Selby, 1978. Of those, the committee found the Pollard and Selby case report the most relevant. (*Id.*) However, the committee specified that all three case reports documented GBS occurring "within an appropriate latency" of between five days and six weeks. (*Id*.) The Pollard and Selby case report was considered the most noteworthy because the subject "received the tetanus toxoid on

three separate occasions over a period of 13 years, and following each vaccination a self-limited episode of clear-cut, well-documented polyneuropathy of the GBS variety ensued." (*Id*. at 87.)

Examining the 2012 report, the first difference of note is that the 2012 report shifted the examination of the Pollard and Selby case report to a discussion of CIDP rather than examining it as evidence relating to GBS. (2012 IOM Report, *supra,* at Ex. E, p. 559.) However, it does not necessarily appear that this change alone explains the difference in conclusion.[34] Apart from Pollard and Selby, the 2012 report examined a total of ten case reports under its assessment of mechanistic evidence for GBS. (2012 IOM Report, *supra,* at Ex. E, pp. 557-58.) This included the Hopf and Newton and Janati case reports previously considered by the 1994 report. (*Id*.) However, the 2012 report concludes that none of the case reports contributed to the weight of mechanistic evidence. (*Id*. at 558.) String citing all ten of the case report publications, it indicates that the reports "did not provide evidence beyond temporality" and that "[l]ong latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes." (*Id*.) This is the limit of any criticism of either the Hopf or Newton and Janati case reports in the 2012 report, though the prior 1994 report had previously adjudged these care reports to be post-vaccination GBS and confirmed the appropriateness of the latencies in each case.

Thus, the difference in view between the 1994 and 2012 IOM reports turns largely on a very narrow weighing of three case reports rather than on the availability of any substantial new evidence. And, as the 2012 report explained, such weighing involves "elements of expert clinical and scientific judgment." (2012 IOM Report, *supra,* at Ex. E, p. 24.) That is, the IOM effectively acknowledges in many cases there will not be a clearly or self-evidently correct interpretation.

In any event, the actual conclusion of the 2012 IOM report is that the evidence is "inadequate to either accept or reject a causal relationship" between tetanus-containing vaccines and GBS, which should not be confused with a conclusion that the evidence *favors rejection* of a causal relationship. (2012 IOM Report, *supra,* at Ex. E, pp. 15,

[34] The 2012 IOM report separately defines GBS and CIDP respectively as acute and chronic immune-related disorders of the peripheral nerves. (2012 IOM Report, *supra,* at Ex. E, pp. 637, 639.) However, while the 1994 report did discuss GBS specifically, it premised its discussion on the biological plausibility of vaccine-caused demyelinating disorders generally and did not include any separate discussion of CIDP. (1994 IOM Report, *supra,* at Ex. G, p. 88.) Moreover, the diagnostic criteria for GBS discussed in the 1994 report considers either prolonged progression or relapse to be a clinical variant of GBS. (1994 IOM Report, *supra,* at Ex. G, p. 41.) Apart from Pollard and Selby, two other case reports referenced in the 1994 report's discussion of GBS (Reinstein et al., 1982; Quast et al., 1979) are discussed in the 2012 report's discussion of CIDP. Two case reports (Quast et al., 1979; Pritchard, 2002) are included in the 2012 reports' discussions of both CIDP and GBS. (2012 IOM Report, *supra,* at Ex. E, pp. 557-59.) Moreover, the 2012 report cites the same mechanistic language for both GBS and CIDP (*i.e*., that autoantibodies, T cells, and molecular mimicry may explain the symptoms of CIDP). And, in any event, given that the 2012 report concluded that none of the case reports addressed under either category, GBS or CIDP, contributed to the weight of mechanistic evidence, reshuffling the case reports among the two categories would not change the outcome.

558.) The IOM is very clear in explaining that "the committee began its assessment from the position of neutrality; until all evidence was reviewed, it presumed neither causation or lack of causation. The committee then moved from that position only when the combination of epidemiologic evidence and mechanistic evidence suggest a more definitive assessment regarding causation, either that the vaccines might or might not pose an increased risk of adverse effect." (*Id*. at 15.) The committee specifies that a conclusion that there is inadequate evidence to accept or reject a causal relationship is confirmation that the committee never "shift[ed] away from the neutral position." (*Id*.) Thus, petitioner is persuasive in contending that the IOM's 2012 conclusion inherently does not constitute any refutation of the earlier report. (ECF No. 77, p. 8.)

In sum, the 1994 and 2012 reports represent two separate judgments by two independent expert committees regarding much of the same basic underlying data. For the reasons discussed above, respondent is not persuasive in suggesting that the earlier report is either formally superseded or inherently outdated. Thus, the 1994 report, and its expert conclusion that there is evidence to favor a causal relationship between tetanus-containing vaccines and GBS, does constitute some evidence supportive of petitioner's *Althen* prong one showing, albeit tempered by the fact that this conclusion has not been consistently stated by the IOM.

iii. Petitioner's Experts Are Persuasive in Opining that the Tdap Vaccine Can Cause GBS

Finally, the remaining question is whether petitioner's experts are persuasive in building upon all of the above to further assert that the Tdap vaccine at issue in this case can cause GBS. On that question, petitioner's experts rely on the following additional points that I find persuasive when considered in light of the above-discussed background:

- According to the IOM, "the effects of natural infection [represents] one type, albeit minor, of clinical or biological evidence in support of mechanisms." (2012 IOM Report, *supra,* at Ex. E, p. 13.) In that regard, the IOM explains that diphtheria infection can lead to neuropathy in up to 75% of severe infections and tetanus infection can likewise lead to neurologic damage. (2012 IOM Report, *supra*, at Ex. E, pp. 526, 528.) Further to this, Dr.Shafrir has highlighted literature showing that tetanus infection can cause peripheral neuritis generally and that GBS in particular has been documented as a complication of tetanus infection. (Ex. 15, p. 34 (citing Shahani et al., *supra,* at Ex. 38; Lee et al., *supra,* at Ex. 39).) This is comparable to the logic Dr. Platt applies in preferring streptococcal infection as a cause of GBS. (*Compare* Shahani et al., *supra,* at Ex. 38, Lee et al., *supra,* at Ex. 39, *and* Yuki & Hirata, *supra,* at Ex. M.)

- A number of individual case reports specifically implicate vaccines containing tetanus and diphtheria in GBS. (Ex. 15, p. 33 (citing Exs. 28-33).) This includes the Newton and Janati and Pollard and Selby case

reports (Exs. 31, 33) reviewed by both of the above-discussed IOM reports as well as the Baust, Pritchard, and Bakshi and Graves case reports (Exs. 29, 32, 34) considered by the 2012 IOM report only. Dr. Shafrir additionally cites four cases of GBS from Thailand following dT vaccine reported in 2014 and an additional 2011 report of GBS following Tdap vaccine. (Exs. 28, 30.) Drs. Benson and Platt both reject the value of case reports categorically without offering any specific critique of the case reports filed in this case. (Ex. A, pp. 5 (Dr. Benson criticizing Dr. Shafrir for relying on "predominantly small scale, basic science" in lieu of epidemiology); Ex. C, p. 6 (Dr. Platt indicating that "to establish causality, case reports alone are not sufficient" and turning to epidemiology).) This is unpersuasive. Although case reports are of variable quality and context is significant, both the IOM and program caselaw suggest that case reports can sometimes have value when coupled with other evidence and cannot be reflexively disregarded.[35] (1994 IOM Report, *supra,* at Ex. G; 2012 IOM Report, *supra,* at Ex. E.) Moreover, the 1994 IOM committee found value in at least some of these reports. Dr. Platt's summary dismissal of the case reports supporting vaccine causation is especially unpersuasive because he himself otherwise affirmatively relies on case reports in the absence of epidemiology to assert strep infection as a cause of GBS. (Ex. C, p. 10 (citing Ex. M).)

- While Dr. Benson criticizes Dr. Shafrir's "basic science literature," she also concedes that the Bavaro study demonstrates "some homology between diphtheria and myelin associated proteins, [though] no large scale human data is presented." (Ex. A, p. 6; Simona Bavar et al., *Pentapeptide Sharing Between Corynebacterium Diphtheria Toxin and the Human Neural Protein Network,* 33 IMMUNOPHARMOL. & IMMUNOTOXICOL. 360 (Ex. 51).)

- Several pieces of literature regarding management of inflammatory neuropathies express caution regarding exposures to tetanus-containing vaccines. (Ex. 15, p. 34 (citing Hadden & Hughes, *supra,* at Ex. 35, p. 5 (explaining that "the risk of relapse following immunization after GBS or CIDP was low but not absent . . . [for CIDP] the use of tetanus toxoid causes particular concern.")); Lu & Zhu, *supra,* at Ex. 46, p. 4 (stating that

[35] Case reports "'do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value'. . . [but] 'the fact that case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight.'" *Paluck v. Sec'y of Health & Human Servs.*, 104 Fed. Cl. 457, 475 (2012) (quoting *Campbell v. Sec'y of Health & Human Servs.*, 97 Fed. Cl. 650, 668 (2011), *aff'd*, 786 F.3d 1373 (Fed. Cir. 2015)). Case reports often present a detailed report of symptoms, signs, diagnosis, treatment, and follow-up care. Oftentimes petitioners in the Program will highlight the usefulness of case reports in cases of novel, unusual or rare diseases. *See Patton v. Sec'y of Health & Human Servs.*, 157 Fed. Cl. 159, 166-67 (2021). *But see Crutchfield v. Sec'y of Health & Human Servs.*, No. 09-39V, 2014 WL 1665227, at *19 (Fed. Cl. Spec. Mstr. Apr. 7, 2014) ("single case reports of Disease X occurring after Factor Y . . . do not offer strong evidence that the *temporal* relationship is a *causal* one—the temporal relationship could be pure random chance"), *aff'd*, 125 Fed. Cl. 251 (2014).

"[t]he risk of GBS or CIDP relapse following immunization is low, except for a concern with tetanus toxoid").) Thus, there is evidence that the relevant medical treatment community considers the potential causal relationship to constitute a genuine real-world concern for patients.

b. *Althen* Prong Two

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show [s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. *See* § 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed.Cl. 706, 746 n.67 (2009) ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record—including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 119, 136 (2011), *aff'd*, 463 Fed. App'x 932 (Fed. Cir. 2012); *Veryzer v. Sec'y of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

On the whole, petitioner's treating physicians provide support throughout the medical records in favor of a logical sequence of cause and effect between his July 8, 2015 vaccinations and his GBS. In the most contemporaneous record, on July 9, 2015, Dr. Hernandez wrote "[r]eceived vaccine yesterday, left facial drooping and ting[l]ing hands and feet . . . 11 [year old] male presents to the ED with mother [complaining of]

left facial drooping onset today . . . Immunization reaction, initial encounter possible." (Ex. 4, pp. 5-8.) On July 11, 2015, Dr. Martinez assessed petitioner with "1. Pain in hands and feet and feet paresthesias . . . 2. [Rule out] infectious process or side effect secondary to vaccine." (Ex. 4, pp. 85-88.) Then on July 11, 2015, Dr. Robert Reid noted "[c]onsider requesting the pediatrician to report this as a potential adverse response to vaccine (VAERS)." (Ex. 4, pp. 58-62.) Still on July 11, 2015, immunologist Dr. Sigua wrote:

> He received the DTaP and meningococcal vaccines on 7/8/15 to his left arm, and later that day reported localized pain . . . Assessment . . . 11 [year old] male presenting with worsening paresthesias, weakness, and bilateral ptosis. These symptoms started within a day after he was administered both the DTaP and meningococcal vaccines. His MRI brain/spine and CSF studies thus far have been unrevealing. There is concern that these symptoms may be related to the recent vaccine administrations.

(Ex. 4, pp. 63-66.) The following day on July 12, 2015, Dr. Martinez "fe[lt] he has an atypical case of GBS in view of symptoms and [history] of vaccine in spite of labs[.] 2. [Rule out] infectious process or side effect secondary to vaccine." (Ex. 4, pp. 96-100.) On July 13, 2015, Dr. Penson submitted a VAERS report. (Ex. 9, pp. 1-2.)

Notably, following the discovery of petitioner's positive strep culture, his treating physicians continued to relate his vaccinations to his GBS. On July 14, 2015, Dr. Adler wrote, "11 [year old] male with atypical GBS likely related to vaccination and opthalmoplegia requiring intubation today for neuromuscular resp[iratory] failure and with autonomic instability and positive throat [culture] for strep pyogenes." (Ex. 4, p. 123.) The following day, July 15, 2015, Dr. Adler noted, "Immunologic [workup] neg[ative] to date. Suspect vaccine assoc[iated] GBS. Strep [culture] positive on throat swab." (*Id.* at 158.) Later, on July 23, 2015, Dr. Deeter noted, "Per immunology and infectious disease, process is likely related to the Menactra vaccination[36] . . . Report has been made to the vaccine adverse event system." (*Id.* at 286.) Finally, in petitioner's discharge summary on July 27, 2015, Dr. Ford stated, "[Infectious Disease]: Throat culture was (+) for Group A Strep and he received a course of Clindamycin (PCN allergy). He completed a course of Doxycycline to cover for tick-born pathogens. Viral and bacterial cultures including CSF were all negative. His case was reported as an adverse reaction to Menactra."[37] (Ex. 4, p. 43.)

Respondent raises three concerns with respect to *Althen* prong two. First and perhaps foremost, respondent contends that the timing of onset relative to vaccination is too short to allow for a logical sequence of cause and effect supporting vaccine causation. (ECF No. 76, p. 15.) This issue is addressed under *Althen* prong three

[36] This appears to be a misstatement insofar as I do not find where any of the infectious disease or immunology specialists indicated any preference for the Menactra over the Adacel vaccine as causal. The specialist notes consistently report both vaccines (Ex. 4, pp. 58-66) and both vaccines were ultimately included in the VAERS submission (Ex. 9).

[37] Again, this is a misstatement insofar as the VAERS report includes both vaccines. (Ex. 9.)

below. Because petitioner has preponderantly satisfied *Althen* prong three, the question of timing likewise presents no barrier to petitioner's claim relative to *Althen* prong two for all the same reasons.

Second, respondent contends that, in any event, the above-discussed treating physician statements are limited to recognizing the coincident timing between vaccination and injury. (ECF No. 76, p. 6, n. 4.) Further to this, Dr. Benson suggested the treating physicians were merely recording a parental concern of vaccine-causation and that "[n]owhere do any of [petitioner's] providers state that they personally attribute his disease to vaccination." (Ex. A, p. 8.) I do not agree with these characterizations. In addition to all of the notations above and the VAERS report, following his initial hospitalization, petitioner's treating physicians specifically included a diagnosis of "Guillain-Barre syndrome following vaccination" among his discharge diagnoses. (Ex. 4, p. 42.) Moreover, the records reflect that petitioner had specialist consultations with both immunology and infectious disease. These consultations took a history of petitioner's activities and health over the preceding months to consider a wide range of potential etiologies. (Ex. 4, pp. 59, 67.) But in any event, even accepting respondent's premise, Dr. Shafrir's expert neurology analysis provides an additional unambiguous causal opinion.

Third, respondent stresses that infectious agents "have a well-established link with GBS supported by epidemiologic and mechanistic evidence." (ECF No. 76, p. 15.) In petitioner's case, respondent contends that further infectious causes were not ruled out—leaving open the possibility that a gastrointestinal or upper respiratory infection (e.g., strep), could have caused petitioner's GBS. (*Id.*) Respondent highlights a note from July 17, 2015, where petitioner's neurologist noted that petitioner had a strep infection prior to the onset of GBS and questioned whether it could have triggered his illness. (*Id.* (citing Ex. 4, p. 75).) Respondent also stresses that infections, unlike vaccines, have been identified as causes of some immune-mediated disorders and feature antigen persistence, epitope spreading, pathogen replication—making it "far more likely that an infection triggered petitioner's GBS." (*Id.*)

Among published case series, approximately two-thirds of all cases of GBS are preceded by a gastrointestinal or respiratory infection within three months prior. (Baxter et al., *supra,* at Ex. II; Ropper et al., *supra,* at Ex. 21.) *Campylobacter jejuni*, cytomegalovirus (CMV), Epstein-Barr virus, and *Mycoplasma pneumoniae* are known precipitants of GBS, with other infections occurring no more often in GBS than in controls. (Ropper et al., *supra,* at Ex. 21.) However, Dr. Benson and Dr. Platt's opinions that they cannot rule out the possibility of an infectious cause is not strong evidence. While Dr. Platt indicates that "[g]roup A strep infection has been reported as a potential cause of Miller Fisher variant GBS," he also acknowledges that it is "certainly not a common trigger." (Ex. C, p. 11.) And, while respondent relies heavily on the idea that infections generally have characteristics that make them more likely causes of GBS, the evidence implicating *this type of infection* is very limited. (*See* Yuki & Hirata, *supra,* at Ex. M.) No other type of infection is evidenced as even potentially present.

Additionally, Dr. Platt references literature which suggests that "antecedent infection is noted two to four weeks prior to the onset in most GBS." (Ex. C, p. 11 (citing Dimachkie & Barohn, *supra,* at Ex. S).) As discussed relative to *Althen* prong three below, Dr. Platt repeatedly emphasizes that illness typically precedes GBS by between one to four weeks. (Ex. C, p. 8; Ex. RR, p. 10; Ex. UU, p. 4.) Petitioner's throat swab sample was obtained on July 12, 2015, and subsequently cultured on July 14, 2015, which showed moderate growth for group A strep (*Streptococcus pyogenes*). (Ex. 4, p. 576.) Dr. Platt argues that petitioner had strep infection prior to hospitalization.[38] (Ex. C, p. 9.) However, it is unclear, from these records alone, when petitioner acquired the streptococcus infection, as the only notation of a sore throat in the medical records was reported on July 11, 2015, in the context of petitioner's intubation. (*See* Ex. 4, p. 79.) On July 8, 2015, the day petitioner received the vaccines in question, he had a well-child visit where no complaints or symptoms of illness were noted. (Ex. 2, pp. 61-63.) Moreover, the history provided during petitioner's infectious disease consult indicated that during the month prior to his GBS, petitioner had been camping and vacationing with no mention of any illness. (Ex. 4, pp. 59, 67.) Accordingly, there is not preponderant evidence establishing the infection to have occurred within a timeframe that respondent's experts would agree is medically reasonable to infer causation.

c. *Althen* prong three

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 Fed. App'x 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014). In this case, this analysis involves two disputed points. First, what actually was the latency between vaccination and onset of GBS in this case? Second, can the vaccine(s) at issue cause GBS in that amount of time?

With regard to the first question, there is little debate between the parties as to the first relevant symptoms. Both parties' neurology experts agree that onset of weakness and progressive neurologic decline began on July 10, two days post-vaccination (Ex. 15, pp. 29, 35, Ex. A, p. 3), but both parties also identify numbness and tingling (paresthesia) in petitioner's hands and feet occurring the day prior as his first

[38] Dr. Platt relies on a single citation to a medical record from July 17 that indicates a possible prior strep infection at some unspecified time "prior to this illness." (Ex. C, pp. 9-10.)

symptoms of GBS (Ex. 15, p. 31; Ex. A, p. 5). I agree.[39] The parties differ, however, regarding when on July 9 those first symptoms of numbness and tingling began. Based on my review of the record as a whole, the evidence preponderates in favor of a finding that onset of petitioner's symptoms of numbness and tingling, and thereby his GBS, occurred during the evening of July 9, 2015, a little more than 24 hours post-vaccination.

Dr. Benson opines for respondent that onset was *less than* 24 hours post-vaccination based on later histories that placed onset of extremity tingling earlier in the day on July 9. (Ex. A, pp. 2-3, 6 (citing Ex. 4-1, pp. 56, 43, 64, 73, 150).) However, this earlier onset is not preponderantly established. These later histories are not uniform in their details.[40] Thus, Dr. Benson acknowledges that petitioner's course during the afternoon of July 9 is "unclear" with "variable accounts" contained in the records. (*Id*.) In contrast, the record of petitioner's first ED encounter is very clear in explaining that when petitioner first presented for symptoms of ptosis and numbness and tingling, these symptoms arose for the first time when he awoke from his afternoon nap that *began* at 4pm, about 24 hours post vaccination.[41] (Ex. 4, p. 5.) That record explicitly explains that when petitioner was picked up from band camp on July 9, he complained of post-injection arm pain for which his mother provided Ibuprofen. Then, he "went to sleep and when he woke up, mom noticed his left eyelid appeared to be 'drooping.' He also [complained of] tingling and numbing sensation to his bilateral fingertips extending to his wrists and as well his toes extending all over the [sic.] both feet." (*Id*.) Although later reports are variable and inconsistent regarding onset of these

[39] According to the literature, the most common initial symptom of GBS is acroparesthesia, tingling in the hands and feet, particularly the fingers and toes, with little objective sensory loss. (Dimachkie & Barohn, *supra,* at Ex. K, p. 3; *see also Acroparesthesia,* DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=724&searchterm=acroparesthesia (last accessed Feb. 17, 2023).) Although Dr. Shafir suggests that petitioner's ptosis should not be viewed as part of his GBS (Ex. 15, p. 29), it is not necessary to resolve this question as I find that petitioner concurrently experienced onset of numbness and tingling. Accordingly, even discounting the possibility that the ptosis was an early symptom of the GBS, that would not change the assessment of onset. Facial nerve involvement occurs in up to 70% of GBS cases. (Dimachkie & Barohn, *supra,* at Ex. K, p. 3.) Although petitioner first experienced soreness in the arm in which his vaccines were administered and had some indications of fatigue, there is not preponderant evidence this was related to his GBS, with the arm soreness especially likely to have been an unrelated vaccine reaction. (Ex. 15, p. 30; Ex. A, p. 5.)

[40] For example, one of these histories indicates that petitioner had tingling in his fingers and toes and shooting pains when he left for band camp on July 9. (Ex. 4, p. 42.) Another indicates that the morning of July 9 "he didn't want to get up or talk," but that his shooting pains began "at noon." (*Id*. at 55.) A third indicates onset of numbness and tingling developed at camp, but pain in the hands and feet is first mention after his subsequent nap. (*Id*. at 63.) A fourth indicates that he experienced pain in his hands that day, but makes no mention of numbness or tingling. (*Id*. at 72.) These same histories are also inconsistent regarding the onset of ptosis. (*Compare* Ex. 4, p. 42 (ptosis noted upon being picked up from camp) and p. 55 (onset of ptosis noted only to be on Thursday) and p. 63 (ptosis noted upon waking from afternoon nap).

[41] Although an exact time of vaccination does not appear to be indicated in petitioner's medical records, the records of his July 8, 2015, primary care appointment indicate that his blood was drawn at 4:45 PM. (Ex. 2, p. 63.)

complaints, the promptness with which petitioner's parents sought emergency medical care means that the initial history was recorded mere hours after they first became aware of petitioner's symptoms.[42] This is also consistent with the affidavit account provided. (Ex. 13, p. 1.) Moreover, all of the other experts in the case apart from Dr. Benson assessed onset as having occurred one full day after vaccination. (Ex. 15, p. 30 (Dr. Shafrir indicating onset is "late evening or the night of 7/09/2015"); Ex. 120, p. 5 (Dr. Akbari stating onset is "approximately 24 hours" post-vaccination); Ex. C, p. 7 (Dr. Platt asserting that both ptosis and paresthesia were both documented "one day (approximately 24 hours) after vaccination").)

The next question is whether a one-day period of onset is medically appropriate to infer vaccine causation. On this question, all agree that the onset in this case would be atypically rapid if the GBS were caused by the vaccinations at issue. However, petitioner's experts provide several reasons for concluding that the rapid onset should still be considered medically appropriate.[43] Respondent's experts, by contrast, focus almost exclusively on what is *typical* rather than what is possible or medically reasonable and neither clearly articulates what they consider to be a minimum latency, making it more difficult to assess and accept their competing opinions. In particular, Dr. Platt explains that "[e]ven if it were established that tetanus and/or meningococcal vaccination could cause GBS, the timing of the symptoms further weakens any potential link. The reason why vaccine causality is unlikely in this case (perhaps unintuitively to those not familiar with this literature), is that the symptoms started the day after vaccination. When an infectious trigger is identified, it is *typically* between 1 to 4 weeks between this antecedent infection and onset of weakness." (Ex. C, p. 8 (citing Jacobs, et al., *supra,* at Ex. I (emphasis added)).)[44] Dr. Platt stresses this "typical" timeframe repeatedly throughout all of his reports. (Ex. C, p. 8; Ex. RR, p. 10; Ex. UU, p. 4.)

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[42] Petitioner first presented to the emergency department on July 9, 2015, at 10:37 PM with a chief complaint of facial drooping along with numbness and tingling in his hands and feet. (Ex. 4, p. 5.) These symptoms were first observed following a 4:00 PM nap on July 9, 2015. (*Id.*) Petitioner averred that the nap lasted for three hours (Ex. 13, p. 2), which is likely consistent with petitioner's 10:37 PM presentation time. (Ex. 4, p. 5.)

[43] Because the 1994 IOM report was discussed extensively with regard to *Althen* prong one, I note in the interest of completeness that the 1994 committee indicated that the minimum latency for GBS is 5 days. (1994 IOM Report, *supra,* at Ex. G, p. 45.) However, there are several reasons why this is not dispositive. First, the authors characterized this only as a "conservative estimate" rather than any confirmed latency period. (*Id.*) Additionally, this specific estimate was premised on a delayed hypersensitivity mechanism. (*Id.*) However, that is not the limit of what the report concluded was the biologically plausible as a mechanism of vaccine-caused demyelination. (*Id.* at 48.) Further, this *Althen* prong three analysis also discusses a substantial amount of additional literature discussed by petitioner's experts that post-dates the 1994 report.

[44] Dr. Platt's reliance on Jacobs et al. is itself less persuasive insofar as the Jacobs study itself does not address timing of onset nor include specific findings regarding timing. Dr. Platt's reference derives from a statement in the introduction that notes GBS to follow infection in two-thirds of cases and that among such cases there is an "interval of 1 to 4 weeks between antecedent infection and onset of weakness." (Ex. I, p. 2.) However, this leaves fully one-third of cases unaddressed. Dr. Shafrir likewise acknowledges that a majority – about 60% - of cases of GBS will fit this pattern. (Ex. 15, p. 32.) Moreover, other evidence of record discussed below suggests that this statement is an oversimplification and/or overgeneralization.

Dr. Shafrir explains, however, that GBS "is not a uniform entity." (Ex. 15, p. 30.) He explains that it is a pathological process affecting the peripheral nerves via different mechanisms. He indicates that GBS represents an autoimmune process whereby different antibodies may variously affect the nodes of Ranvier, myelin, or nerve axons. (*Id*. at 30-31.) Thus, when speaking of GBS as single entity, it reflects a variable clinical course. (*Id.*) Additionally, both Dr. Shafrir and Akbari stressed the importance of genetic susceptibility with respect the variety of presentations seen among GBS patients. (Ex. 15, pp. 36-37; Ex. 65, pp. 13-14.) Initially, Dr. Shafrir specifically invoked genetic susceptibility as a factor that may help explain the rapid onset in this case, noting that the timing and intensity of antibody production is genetically controlled. (Ex. 15, p. 37.) Dr. Akbari later opined that "[h]ost susceptibility to the development of GBS is arguably one of the most important factors in the development of GBS independent of the initiating pathologic cause." (Ex. 65, p. 13.) And, indeed, Dr. Platt confirmed his agreement with this broader point, noting it to be "accurate." (Ex. RR, p. 7.) Dr. Shafrir acknowledges, as Dr. Platt stresses, that 60% of GBS cases are preceded by an infection occurring weeks prior to onset (Ex. 15, p. 32); however, he also cites a number of studies wherein GBS has been attributed to either illnesses or vaccinations that occurred within days prior to onset, including some cases where onset of GBS was within one day of the antecedent event. (*Id.* at 36.)

For example, petitioner has filed one study by Takahashi et al. that showed that among over one hundred GBS patients who experienced their condition following confirmed *c. jejuni* infection (an acute gastrointestinal illness), onset of neurological symptoms occurred from between one- and 24-days following onset of diarrhea, with a median onset of ten days post-diarrhea onset. (Takahashi et al., *supra,* at Ex. 59, p. 4.) This not only shows at least some cases of GBS to have occurred within one day of a generally well-established and clinically confirmed antecedent, but also more generally presents a data curve embracing a shorter onset period than what Dr. Platt suggests by citing a one-to-four-week period as "typical." (*Id.* at 3 (Fig. 5).) Similarly, another paper filed by respondent examined six prior studies with regard to the timing of onset of the Miller Fisher variant of GBS, finding that the *mean* time from preceding illness to onset of GBS symptoms varied by study from between 3.5 and 10 days with an overall mean of 8.1 days. (Masahiro Mori et al., *Fisher Syndrome: Clinical Features, Immunopathogenesis and Management,* 12 EXPERT REV. NEUROTHERAPEUTICS 1, 5 (2012) (Ex. N) (Table 1).) For the mean latency to have been 3.5 days, at least some of the cases involved must necessarily have had onsets shorter than 3.5 days. Additionally, an overall mean of 8.1 days among all the studies suggests an earlier "typical" onset than what Dr. Platt urges. This is repeated by another study filed by respondent which indicated an onset range of 1 to 30 days with a median latency of 8 days. (Masahiro Mori et al., *Clinical Features and Prognosis of Miller Fisher Syndrome,* 56 NEUROLOGY 1, 1 (2001) (Ex. O).)

Additionally, two more pieces of literature relate this earlier timeframe to vaccinations. A 2013 study published in the *American Journal of Epidemiology*

examined the risk of GBS following the 2009-2010 H1N1 influenza vaccination.[45] (Polakowski, *supra*, at Ex. 129.) That study looked at two post-vaccination risk periods, a 1-42 risk period and a narrower 8-21 day period. Although the study found a higher risk within the narrower period, the risk for the 1-42 day period remained statistically elevated after excluding cases with preceding illnesses and adjusting for seasonality.[46] (*Id.* at 7 (Table 4).) A separate chart within the paper confirms this analysis of a statistically significant 1-42 day risk period included cases occurring at one- and two-days post-vaccination. (*Id*. at 6 (Fig. 2).) A 2017 paper examined the clinical characteristics of GBS cases in Korea that had been compensated within Korea's vaccine injury compensation program. (Park, *supra*, at Ex. 58.) Among that population, over 97% experienced onset within three weeks of vaccination and a majority experienced onsets within two days of vaccination. Again, as with the above-discussed study regarding *c. jejuni* infection, this complicates respondent's reliance on a one-to-four-week onset being "typical." Particularly relevant to this case involving a minor vaccinee, the study also found that subjects under 19 years of age experienced faster and more severe courses of GBS. Whereas those over 20 years of age had an interquartile range of onset from three to 15 days post-vaccination, those 19 and under had an interquartile range of onset from only one to three days. (*Id*. at 3.)

Dr. Platt does explicitly state in his fist report that in his opinion a latency of one to two days is "implausible." (Ex. C, p. 5.) However, the basis for that assertion is not fully explained. Dr. Platt never explicitly describes any medically reasonable timeframe to infer causation beyond the one-to-four-week period he repeatedly cites as merely "typical." Noting a statement from one of Dr. Shafrir's citations, Dr. Benson indirectly suggests a minimum latency of four days. (Ex. A, p. 6.) Both Drs. Platt and Benson offer some reference to the relationship between adaptive immunity and autoimmune injury as a reason for questioning the timing of onset in this case. However, without more, respondent's position as to timing is not adequately explained simply by reference to adaptive immunity.

The 2012 IOM report filed by respondent explains that adaptive immunity in general requires a "lag phase" before an adaptive immune response develops that is "classically" believed to be at least four days, but in the case of a repeat exposure may be as little as one day. (2012 IOM Report, *supra,* at Ex. E, p. 88.) After the lag phase, antibodies increase in a logarithmic phase over days until reaching a plateau. (*Id*.) In this case, petitioner's medical records confirm that petitioner had 5 prior vaccinations containing tetanus, diphtheria, and acellular pertussis. (Ex. 1.) Therefore, while commencement of an adaptive immune response is not equivalent to disease onset, general principles of adaptive immunity do suggest that petitioner's adaptive immune response to his Tdap vaccine would have been underway on July 9 when his symptoms began. This is a point stressed by Dr. Shafrir when he raised the issue of immunologic

[45] As explained above (*see* Section II, *supra*) the evidence supporting an association between the 2009 H1N1 influenza vaccine and GBS contributed to the addition of GBS to the Vaccine Injury Table. The Secretary considered the evidence "compelling, reliable, and valid." 2017 WL 202456, at *6295.

[46] This result existed for cases using confidence levels 1-3 of the Brighton criteria for diagnosing GBS.

memory to help explain the onset in this case. (Ex. 15, p. 36.) Thus, for example, Dr. Shafrir also notes that the Vaccine Injury Table allows a minimum latency for post-influenza vaccine GBS of 3 days. (*Id*. at 36.) Further still, he observes that where tetanus-containing vaccines are at issue, the Vaccine Injury Table allows an even shorter latency of 48 hours for immune-mediated injury to peripheral nerves in the form of brachial neuritis.[47] (*Id.* at 33 (citing 42 U.S.C. 300aa-14).) Both of these Table timeframes for peripheral nerve disorders are shorter than what either Dr. Benson or Dr. Platt have acknowledged is possible. (Ex. A, pp. 6-7; Ex. C, pp. 7-8.) While more could surely be said regarding the time needed for an adaptive immune response to develop into an autoimmune injury, respondent's experts have not substantiated any such points on this record.

Additionally, the IOM explains, as Dr. Shafrir likewise highlights in his report (Ex. 15, p. 36), that tetanus-containing vaccines are among a subset of vaccines for which alum adjuvant "may directly activate cells of the innate immune system through its effect on local inflammasome complexes leading to the release of inflammatory mediators and enhancement of the immune response." (2012 IOM Report, *supra,* at Ex. E, p. 59 (internal citation omitted).) The IOM further relates this to its discussion of latency, indicating that cells "classically associated with the innate immune response" contribute to the activation and amplification of the adaptive immune response. (*Id*. at 58.) Further to this, Drs. Shafrir and Akbari opine that although it is ultimately an autoimmune disorder involving adaptive immunity, onset and symptom presentation of GBS in particular should not be viewed strictly in terms of the adaptive immune response. Specifically, Dr. Shafrir explains that multiple articles indicate that the innate immune system plays an important role in the pathogenesis of GBS, noting especially that the AIDP form of GBS that petitioner had is considered more T cell dependent as compared to the AMAN type of GBS that is considered more antibody dependent. (Ex. 15, p. 33.) Dr. Shafrir also stresses that petitioner's initial presentation of a local vaccine reaction (arm pain) and his early fatigue suggest he was experiencing a robust innate immune reaction to his vaccination. (*Id.* at 30.)

Dr. Akbari also explains that more recent literature describes a category of "fast acting" innate like lymphocytes, which includes gamma delta T cells. According to Dr. Akbari, gamma delta T cells have been seen in nerve biopsies of AIDP patients and have the ability to directly promote molecular mimicry. (Ex. 120, p. 3.) Dr. Platt responds that "[w]hile the timeline between vaccination and disease onset is theoretically possible by invoking innate immune cells, there is no evidence provided

[47] The exact pathophysiological mechanism in brachial neuritis is unknown, but immune triggers are suspected, as well as infection, mechanical factors, (repetitive or strenuous motor tasks), and individual (genetic susceptibility. (JJ Jeroen et al., *Neuralgic Amyotrophy: An Update on Diagnosis, Pathophysiology, and Treatment,* 53 MUSCLE NERVE 337 (2016) (Ex. 27).) Biopsies of patients with brachial neuritis have shown epineural perivascular mononuclear T-cell infiltration and active multifocal axonal degeneration without vessel wall inflammation or necrosis. (*Id.* at 340.) A further study reported a decrease in peripheral blood CD81 T-suppressor cytotoxic lymphocytes in the acute phase, which is also seen in GBS and facial nerve palsy. (*Id.*) Taken together, researchers suspect an immune-mediated origin. (*Id.*)

that these cells are actually involved in GBS pathogenesis, so this remains an entirely theoretical model." (Ex. RR, p. 10.) However, Dr. Platt's own citation indicates that gamma delta T-cells "have been shown to play a central role in the pathogenesis of GBS" and also that the gamma delta T-cells have also been shown to react to myelin proteins.[48] (Manuel Rojas et al., *Molecular Mimicry and Autoimmunity,* 95 J. AUTOIMMUNITY 100, 104 (2018) (Ex. L).)

In light of the above, Drs. Shafrir and Akbari have provided seemingly reputable bases for opining that onset of GBS within one day of vaccination can be viewed as medically appropriate despite being atypical while respondent's experts have failed to refute that assertion on this record. Moreover, petitioner's experts' view is apparently shared by petitioner's treating physicians. Despite being aware of the rapid timing of onset relative to vaccination, petitioner's own treating physicians explicitly diagnosed him with "Guillain-Barre syndrome following vaccination." (Ex. 4, pp. 42, 125, 140.) It is also difficult to separate respondent's experts' conclusions with respect to *Althen* prong three from their conclusions regarding *Althen* prong one, which have already been addressed above and found less persuasive. In his first report Dr. Platt quotes Dr. Shafrir's statement that "[i]mmunization is a well-known trigger for Guillain-Barre syndrome and its variants." (Ex. C, p. 5 (quoting Ex. 15, p. 32.) In response, he writes: "If this were true, it would stand to reason that petitioner's symptoms may simply be atypical in that they began prior to the expected time window." (Ex. C, p. 5.) Thus, while he would still clearly find it irregular, it is far from clear that Dr. Platt would treat the timing of onset in this case as dispositive if he were otherwise convinced that the vaccine(s) at issue can in general cause GBS.[49]

While the petitioner in this case has preponderantly satisfied *Althen* prong three despite an atypically rapid onset of just one day, this is a close call and the conclusion is a function of the specific record in this case. The conclusion that a one-day onset is medically appropriate for post-vaccination GBS is not unprecedented, but neither is it the norm. Of the few GBS non-Table claims adjudicated in the Program where onset occurred earlier than three days after vaccination most have not succeeded.[50] On a

[48] In his final report, Dr. Platt ultimately concedes that the literature does support a role for delta gamma cells in the pathogenesis of GBS, but limits his acceptance of that premise to the specific context of molecular mimicry following c. jejuni infection and reiterates his reliance on a "typical" onset period of between one to four weeks between infection and onset of GBS. (Ex. UU, p. 4.)

[49] This point is further evidenced by Dr. Platt's opinion with respect to an alternative cause. Dr. Platt explains in his reports that he finds petitioner's possible strep throat infection to be a more likely cause of his GBS. (Ex. C, pp. 8-10; Ex. RR, p. 10; Ex. UU, p. 7.) However, as explained under *Althen* prong two, above, petitioner's medical records are inadequate to place the onset of his later discovered strep infection. Despite a lack of any information regarding the purported latency, and despite acknowledging that strep infection is "certainly not a common trigger" (Ex. C, p. 10), Dr. Platt finds it a more likely cause because "[i]n contrast to vaccination, where there is negligible evidence of association with GBS, the link between infection and GBS is well-established . . . . " (*Id*. at 8). Dr. Platt makes no specific assertion that petitioner's strep infection occurred between one and four weeks prior to onset of his GBS or, indeed, that the latency can even be determined.

[50] *See Block v. Sec'y of Health & Human Servs.,* No. 19-969V, 2021 WL 5709764, at *4-5 (Fed. Cl. Spec. Mstr. Oct. 29, 2021) (24-hour onset of GBS was not medically-acceptable where petitioner failed to

different record it is likely that I would reach a different conclusion. However, the Federal Circuit holding in *Paluck v. Secretary of Health & Human Services* cautions against setting "hard and fast deadline[s]" for onset. *See* 786 F.3d 1373, 1383-84 (Fed. Cir. 2015) (stating that "[t]he special master further erred in setting a hard and fast deadline" for onset and noting that the medical literature filed in the case "do not purport to establish any definitive timeframe for onset of clinical symptoms."). Moreover, "[t]he Vaccine Act does not contemplate full blown tort litigation in the Court of Federal Claims. The Vaccine Act established a federal 'compensation program' under which awards are to be 'made to vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Knudsen*, 35 F.3d at 549 (quoting H.R.Rep. No. 99–908, 99th Cong., 2d Sess. 18, *reprinted in* 1986 U.S.C.C.A.N. 6344). Accordingly, the Federal Circuit has suggested that this program represents a "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280.

d. Factor Unrelated

Based on the analysis above, petitioner has presented a *prima facie* case that petitioner's GBS was, more likely than not, caused by his Tdap vaccination by demonstrating each of the three *Althen* prongs by preponderant evidence. Once petitioner has satisfied his own burden pursuant under the *Althen* test, the burden shifts to respondent to demonstrate that her injury was caused by factors unrelated to vaccination. § 300aa-13(a)(1)(B); *Deribeaux v. Sec'y of Health & Human Servs.*, 717 F.3d 1363, 1367 (Fed. Cir. 2013).

In order to meet his burden, respondent must demonstrate by preponderant evidence "that a particular agent or condition (or multiple agents/conditions) unrelated to the vaccine was in fact the sole cause (thus excluding the vaccine as a substantial factor)." *de Bazan*, 539 F.3d at 1354. As with petitioner's burden under *Althen*, respondent must show a logical sequence of cause and effect linking the injury to the proposed factor unrelated. *Deribeaux*, 717 F.3d at 1369. It need not be scientifically certain but must be legally probable. *Id*. Significantly, the Federal Circuit has rejected the contention that the presence of a viral infection can *per se* be considered a factor

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establish from an immunologic standpoint how GBS could being in such a short timeframe); *Rowan v. Sec'y of Health & Human Servs.,* No. 2020 WL 2954954, at *16-19 (36-hour post-vaccination onset of GBS for elderly individual was not a medically-acceptable timeframe to support non-Table claim); *Orton v. Sec'y of Health & Human Servs.*, No. 13-631V, 2015 WL 1275459, at *3-4 (Fed. Cl. Spec. Mstr. Feb. 23, 2015) (one-day onset of GBS after flu vaccine administration not substantiated with expert opinion). Still, in one other flu-GBS case the special master found that petitioner preponderantly demonstrated that a 24-hour onset post-vaccination was medically acceptable. *Lehrman v. Sec'y of Health & Human Servs.,* No. 13-901, 2018 WL 1788477 at *16-19 (Fed. Cl. Spec. Mstr. Mar. 19, 2018). Petitioner's expert persuasively explained how his preceding upper respiratory infection acted synergistically with the influenza vaccine, resulting in a rapid onset of GBS. *Id.* at *18. The expert explained that the petitioner's immune system was already activated due to the URI, while the flu vaccine was a subsequent immune challenge which "boosted" the immune response. *Id.* While respondent's expert in that case did not opine that the flu vaccine was in any way associated with petitioner's GBS, he agreed that, though rare, GBS can occur within 24 hours—citing 2% of patients suffered onset of GBS between zero and one day after vaccination in Schonberger's study. *Id.*

unrelated to vaccination. *Knudsen*, 35 F.3d at 548-50. Rather, respondent bears a burden of proving not only that there was a viral infection, but also that the infection was principally responsible for causing petitioner's injury. *Id*.

Here, despite arguing that the inability to rule out infection complicates petitioner's showing under *Althen* prong two, respondent has not offered any argument that the evidence of a step infection is adequate to meet his own burden of proof. (*See* ECF No. 76.) In any event, I conclude respondent has not met his burden of proof for the same reasons discussed within the *Althen* prongs two and three analysis above.

VIII. Conclusion

Accordingly, for all the reasons described above, I find that petitioner is entitled to compensation. Specifically, I find that petitioner has established by preponderant evidence that petitioner's GBS was caused-in-fact by his July 8, 2015 Tdap vaccination. A separate damages order will be issued.

IT IS SO ORDERED.

s/Daniel T. Horner
Daniel T. Horner
Special Master